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# British Heart Journal

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A monthly journal of cardiology
published in association with
the British Cardiac Society

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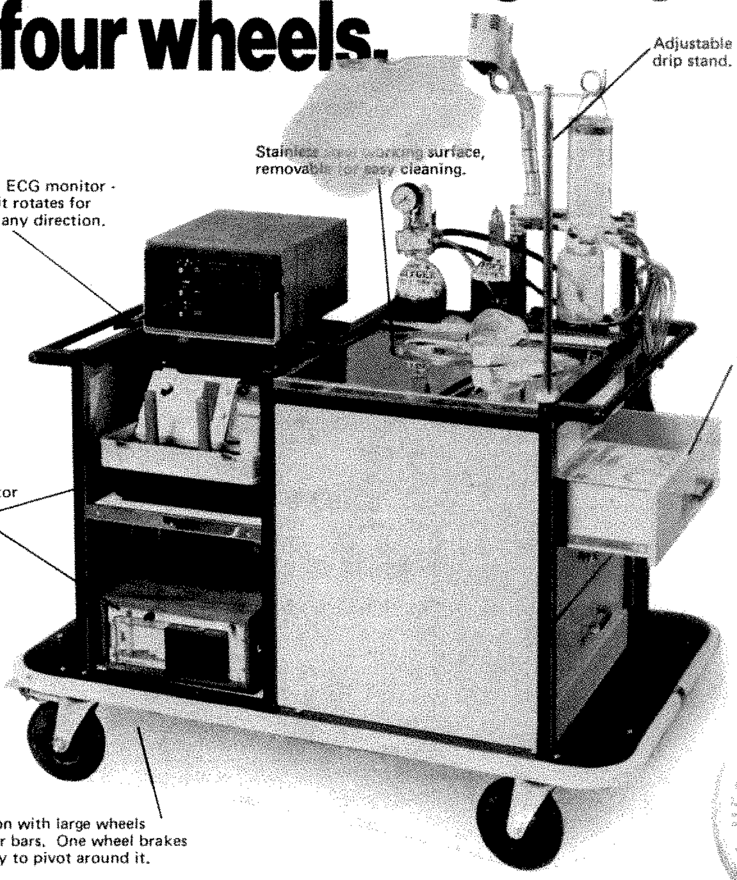

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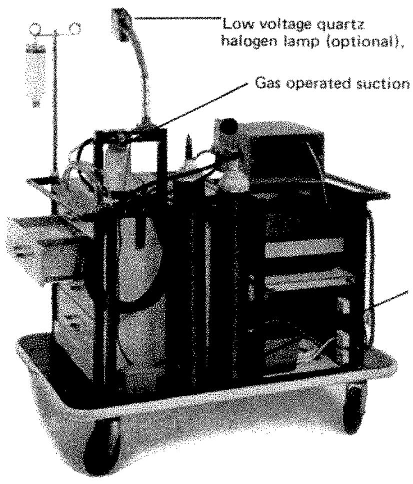

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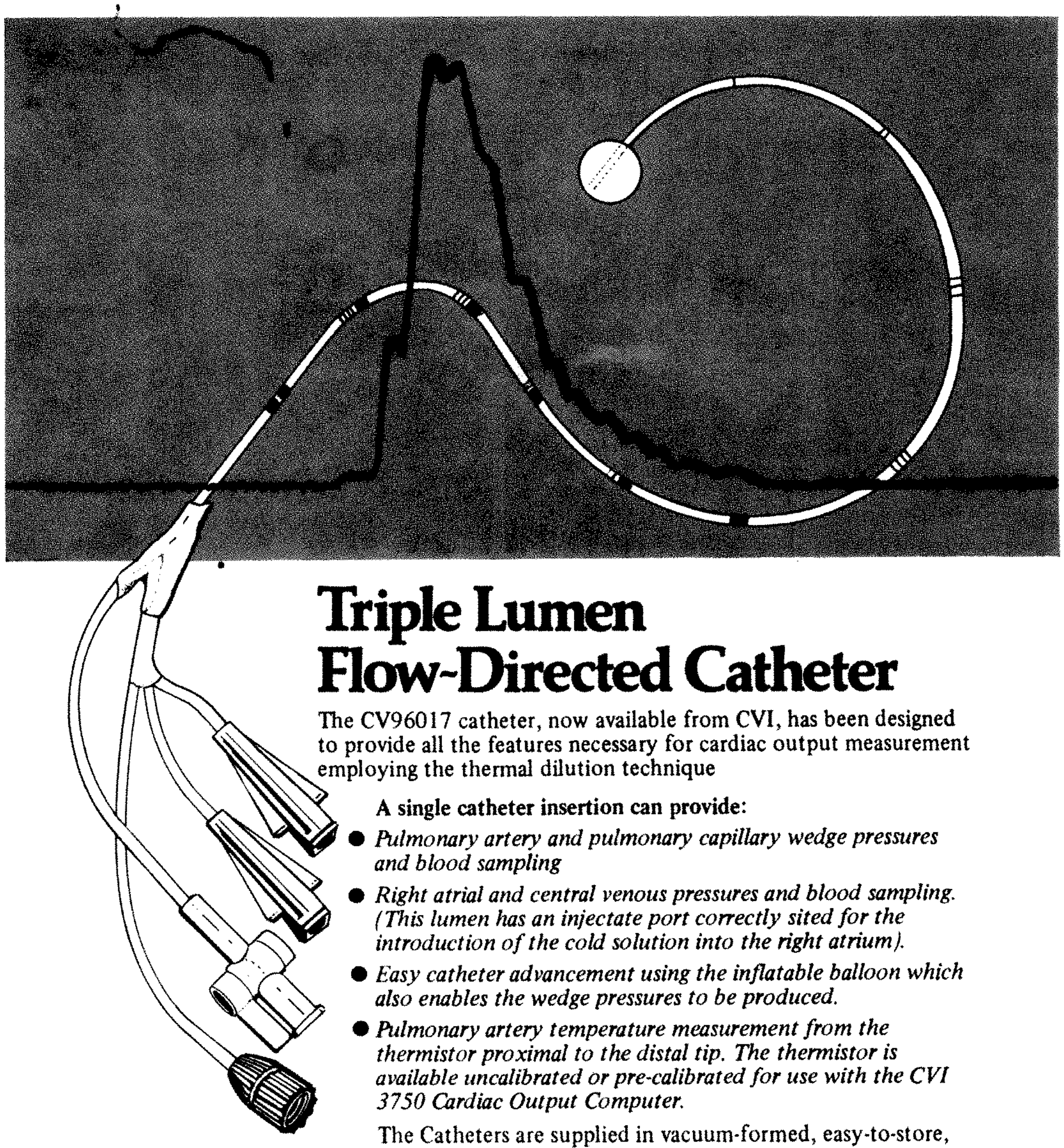

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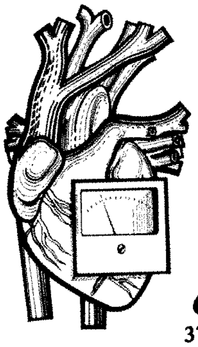

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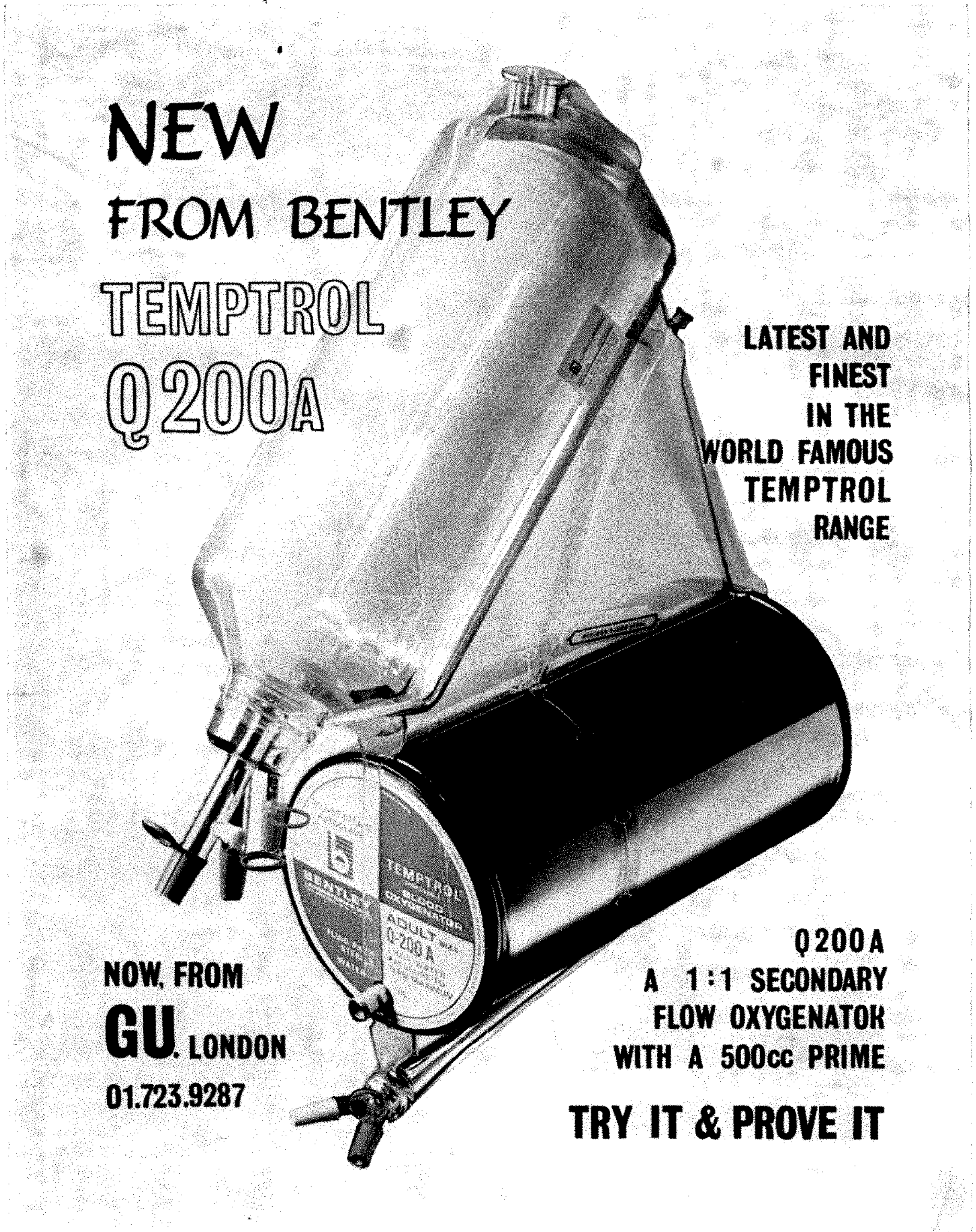

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4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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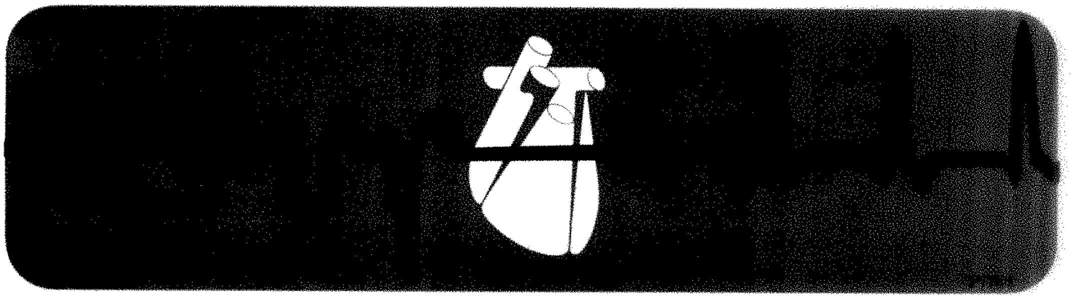

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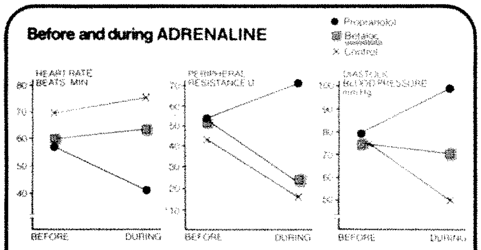

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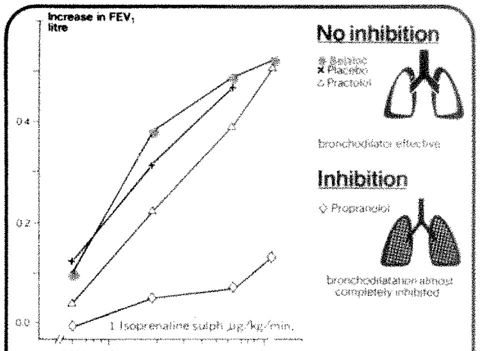

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[1] (1975), *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 University of Gothenburg, Sweden.

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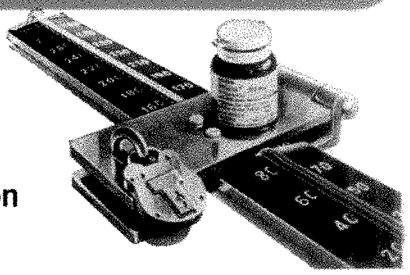

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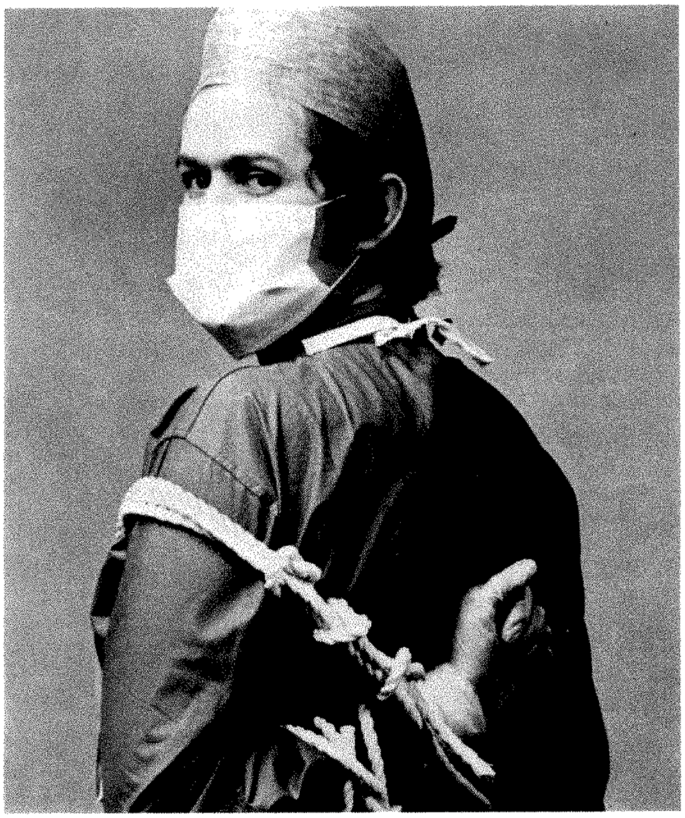

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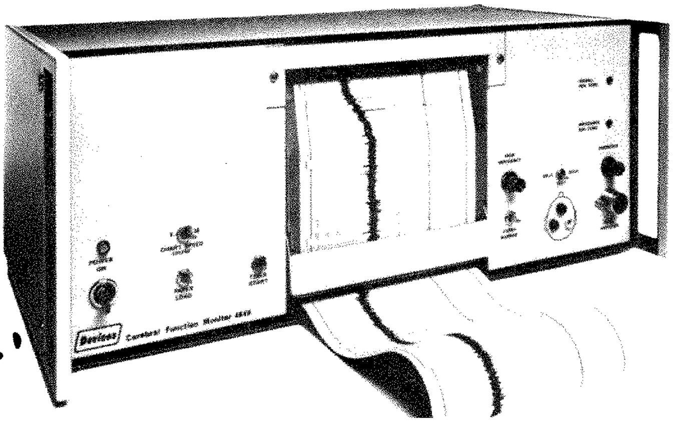

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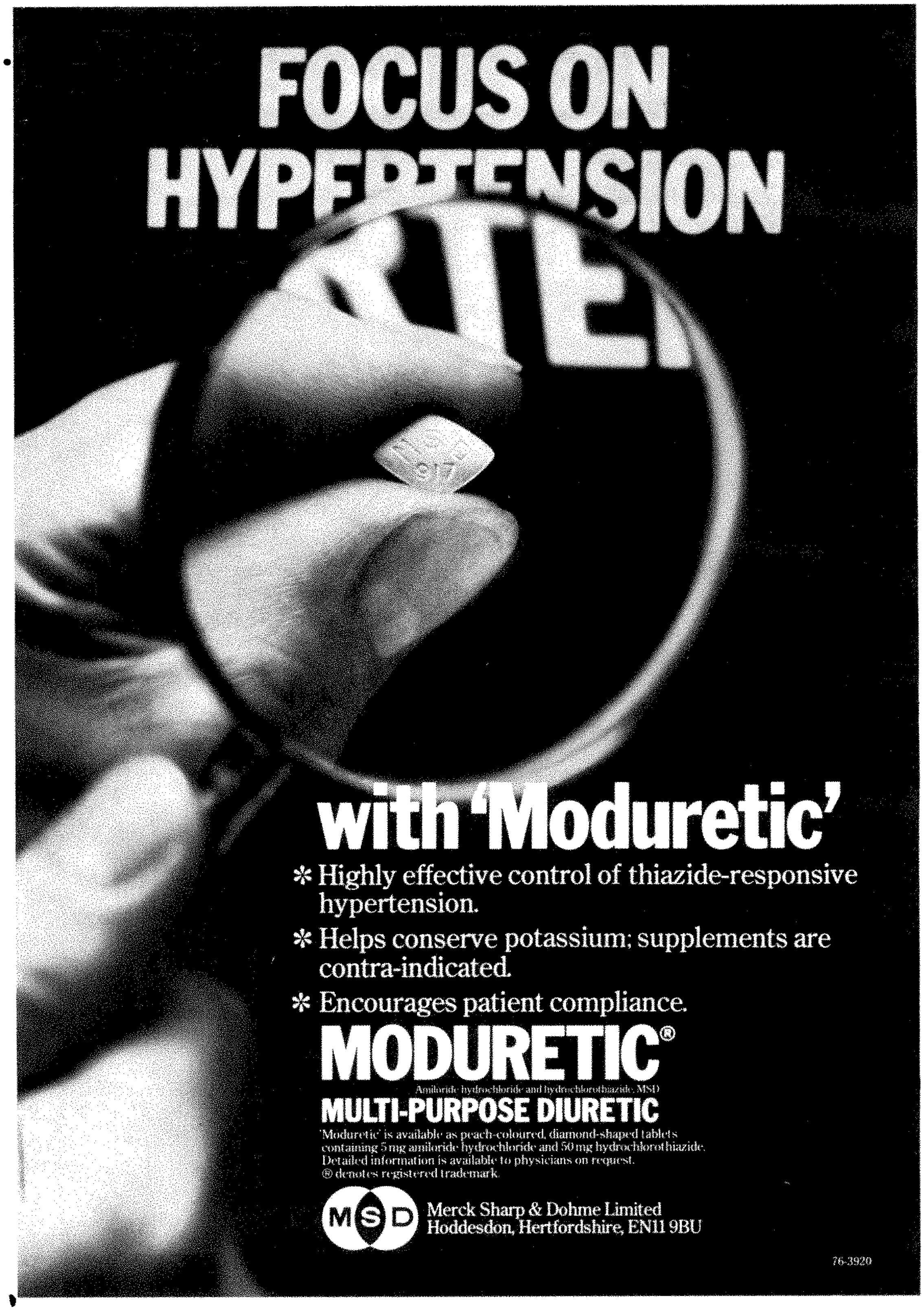

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# HEART JOURNAL

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# Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi

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*Analysis of the pathological findings in 500 cases of fatal acute myocardial infarction showed that in 469 this was localized to one transmural area of the left ventricle; in 31 there was diffuse subendocardial necrosis. In the former occlusive coronary thrombus was found in the related artery in 95 per cent of cases. Variation in the percentage of occlusions found was noted between different prosectors and when coronary artery calcification was present. Only 4 of the 31 patients with subendocardial necrosis had recent occlusion; triple vessel disease was common in this group suggesting general failure of coronary perfusion. It is essential in necropsy studies of the relation of coronary thrombosis to myocardial infarction to be sure that muscle necrosis is present, to distinguish the two forms of myocardial necrosis, and to employ a meticulous dissection technique with decalcification of the arteries when necessary.*

It is hardly credible that there should be continuing debate about what is ostensibly so simple a morphological problem, the relation of coronary thrombosis to acute myocardial infarction. For well over half a century opinion has swung from one extreme to the other and once again it is being suggested, particularly in the United States of America (Roberts, 1974), that the two are not constantly or causally related and even that coronary thrombosis may be a complication of myocardial infarction. The reported proportions of fatal acute myocardial infarcts in which occlusive thrombi are found have varied from less than 50 per cent (Baroldi, 1965; Kagan *et al.*, 1968; Roberts and Buja, 1972) to approaching 100 per cent (Chapman, 1974; Harland and Holburn, 1966). A recent workshop of 10 pathologists (Chandler *et al.*, 1974) in the United States trying to resolve the question succeeded only in once again highlighting the controversy (Burchell, 1974). As pathologists interested in this subject in the United Kingdom, we have reviewed our own necropsy experience of acute infarction in an attempt to identify factors that might explain this wide variation.

## Methods

For this study myocardial infarction was rigidly defined as a localized and discrete area of muscle necrosis in the myocardium visible to the naked eye at necropsy and larger than 3 cm in diameter in one axis. The left ventricular circumference was divided into anterior, posterior, lateral, and septal segments for anatomical definition of the site of localized infarction. No attempt was made to measure accurately the percentage of left ventricular muscle involved in the infarction, though where two or more segments were involved the infarcts were large. Diffuse subendocardial necrosis was rigidly defined to mean circumferential myocardial necrosis involving the inner zone of the whole left ventricle and often the central zone of the papillary muscles. This form of necrosis often associated with additional scattered foci of necrosis up to half a centimetre in diameter is regarded by us as an entity pathologically distinguishable from the localized areas of infarction over 3 cm in diameter.

Over a 10-year period all necropsies were performed by consultant pathologists A, B, C, and D, and a changing population of trainee pathologists under supervision of the consultants and designated as group E. From January 1964 to February 1974 inclusive 6400 routine hospital necropsies were carried out at St. George's Hospital; of these, 500 were performed on patients with myocardial infarction. No forensic necropsies carried out for the coroner are included, all patients having been inpatients of the hospital for a minimum of 24 hours.

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There was no selection of cases by individual pathologists, who are responsible for necropsies on a monthly roster; the different number of necropsies carried out by each merely reflects greater or lesser number of months on the roster. The number of necropsies carried out per year on patients with myocardial infarcts ranged from 43 to 67. Age, sex, and history of hypertension or diabetes were recorded for each patient. Hypertension was defined as blood pressure high enough to have received treatment. The time interval between onset of pain and death was recorded in days.

In this department the standard method of examining the coronary artery tree is by transverse section at 5 mm intervals. Two prosectors (A and B), when there is extensive calcification, routinely decalcify the coronary arteries before transection. In 80 cases post-mortem coronary angiography had been performed before dissection of the heart.

Thrombus was defined as a mass of fibrin and platelets without large numbers of red cells and was regarded as occlusive when completely blocking the lumen of the artery by naked eye examination. Histological examination often reveals some minimal retraction of the thrombus away from the arterial wall; when this led to reappearance of not more than 10 per cent of the lumen, the lesion was still regarded as occlusive. This retraction is at least in part likely to occur in tissue embedding for histological examination.

Occlusive thrombi were recorded as being in the main left coronary artery (L), left circumflex (LC), left anterior descending (LAD), left marginal (LM), right (R), or posterior descending (PD) coronary artery. Our standard necropsy protocol allows a crude pictorial representation of the severity and extent of coronary atherosclerosis and the degree of arterial stenosis; significant stenosis is taken as more than 75 per cent reduction of the lumen.

In common with clinical practice the cases were divided into those with disease affecting one, two, or three major vessels. The left anterior descending, right, and left circumflex are the three vessels considered in this method of assessment. Cases of single vessel disease were divided further into those with a single area of stenosis and those with multiple stenotic areas.

## Results

There were 336 male and 164 female patients. The mean age of male patients was 60, and of female patients 69, at death. Of the total, 25 men (7·4%) and 23 women (14·0%) were diabetic; 80 men (23·8%) and 46 women (28%) had hypertension as previously defined.

### Site of infarction

Of the myocardial lesions, 31 were designated as diffuse, subendocardial necrosis. The site of the remaining 469 localized infarcts, as defined by segment involved, is shown in Table 1. Three infarcts were confined to the right ventricle; all three hearts showed right ventricular hypertrophy. Previous old infarction with fibrous scarring in the left ventricle visible to the naked eye was recorded in 204 of 500 patients (40·8%).

### Frequency and site of occlusive thrombi

In the whole series, 52 (10·4%) had no occlusive thrombi at necropsy. Of 469 patients with localized infarcts, only 25 (5·3%) had no occlusive thrombi. When these results were analysed in relation to which pathologist carried out the necropsy considerable variation emerges (Table 2). The incidence of occlusion in each artery is shown in Table 3.

### Extent of coronary atherosclerosis

Sufficient information for accurate grading of coronary atherosclerosis was available in 448 of these cases; 82 (18·3%) had single vessel disease, 157 (35%) double vessel disease, and 209 (46·7%)

TABLE 1 *Site of infarction: 469 localized transmural infarcts*

| | | | |
|---|---|---|---|
| Anterior | Anterior alone | 127 | 242 |
| | Anteroseptal | 74 | |
| | Anterolateral | 19 | |
| | Anterolateral-septal | 22 | |
| Posterior | Posterior alone | 102 | 167 |
| | Posterolateral | 33 | |
| | Posteroseptal | 24 | |
| | Posterolateral-septal | 8 | |
| Lateral alone | | | 31 |
| Septal alone | | | 3 |
| Right ventricle alone | | | 3 |
| Large infarcts involving over 75 per cent of left ventricle | | | 23 |

TABLE 2 *Analysis of occurrence of thrombi with different prosectors: 469 localized myocardial infarcts*

| | | *Total no. of cases* | *No thrombi found* |
|---|---|---|---|
| Pathologist | A | 131 | 2 (1·5%) |
| | B | 52 | 1 (1·9%) |
| | C | 30 | 0 (0) |
| | D | 81 | 16 (19·8%) |
| Pathologists | E | 175 | 6 (3·4%) |

TABLE 3 *Site of recent coronary occlusion: 469 localized myocardial infarcts*

| | |
|---|---|
| Main left | 15 |
| Left anterior descending or major branch | 219 |
| Left circumflex | 63 |
| Left marginal | 10 |
| Right | 160 |
| Posterior descending | 9 |
| More than one recent occlusion | 31 |

triple vessel disease. Of the 82 patients with single vessel disease, only 18 had occlusions in association with single isolated areas of stenosis.

Severe coronary arterial calcification was noted as a positive finding in 115 cases (23%) of the whole series. Coronary calcification was noted in 17 of the 25 (64%) cases of localized infarction without occlusion.

### Diffuse subendocardial necrosis

Only 4 of the 31 cases of subendocardial necrosis had a recent occlusion. Twenty-eight of the 31 (90%) had triple vessel disease; 23 of the cases had fibrotic areas of healed localized infarction.

### Mural thrombus

Thrombus in the left ventricle was recorded in 139 of the 500 cases (27·8%). Systemic emboli occurred in 48 of the 139, and 24 of these were cerebral.

### External cardiac rupture

A total of 42 patients died as the result of pericardial tamponade; of these 22 (52%) were women and 20 were men (48%). Rupture of the left ventricle was present in 39, of the anterior wall of the right ventricle in 1, and in 2 cases blood appeared to have oozed from the surface of the infarct without frank rupture. The mean age of women dying with tamponade was 74 and of men 68. Cardiac rupture became more common with increasing age in both men and women. Under the age of 70, 10 of 241 men (4·1%) and 7 of 77 women (9·1%) died of cardiac rupture. Over the age of 70, 7 of 87 men (7·9%) and 15 of 95 women (15·7%) died of cardiac rupture. In 33 of these 42 cases, sufficient information was available to assess the degree of atheroma; of these 16 had single, 15 had double, and 2 had triple vessel disease.

### Internal cardiac rupture

Eleven examples of acquired ventricular septal defects were recorded (2·2%) and six of ruptured papillary muscle (1·2%).

### Pulmonary emboli

Major pulmonary emboli were recorded in 56 of the 500 cases (11·2%).

## Discussion

This retrospective study has produced a wealth of data, much of it not controversial. Myocardial infarction is more common in men than women and, on average, occurs a decade earlier in the former than in the latter. It is interesting, but as yet unexplained, that acute myocardial infarction with rupture in the elderly tends to occur with less coronary atherosclerosis than in younger people and in the absence of old infarcts (*British Medical Journal,* 1972). The present study suggests that the risk of external rupture is greater in women than in men at all ages, a fact previously recorded (Mitchell and Parish, 1960). Detailed population rather than hospital study has suggested, however, that in old age, while more cases of cardiac rupture in myocardial infarction are seen in women, the sex and age-corrected incidences are identical (Crawford and Morris, 1960). Haemopericardium may occur occasionally in patients who have no demonstrable cardiac rupture and who may or may not have been treated with anticoagulants (Aarseth and Lange, 1958).

Involvement of the right ventricle in infarcts of the left ventricle is not uncommon, when looked for, particularly in posterior infarcts. On the other hand, isolated right ventricular infarction is decidedly uncommon and is associated in our experience, as in that of others, with right ventricular hypertrophy resulting from severe pulmonary hypertension (Wade, 1959).

The distribution of infarcts and related recent coronary occlusions in our series is much the same as that reported in other published series, but is biased in favour of posterior infarcts because of the number of patients with complete heart block referred to the pacing unit in our hospital. No discordance between infarct site and coronary occlusion was noted and we have found no evidence to support the concept of paradoxical infarction.

The major point at issue is the incidence of recent occlusive coronary thromboses and their relation to myocardial infarcts. This study suggests a constant and probably causal link between occlusive coronary thrombosis and acute infarction. Other workers have not found this relation; explanations must be sought to account for these conflicting observations. First, it seems essential that a rigid definition of acute myocardial infarction be adopted, as in this study, where we used the term in its exact pathological meaning as an easily demonstrable localized area of muscle death. For this to be easily visible the patient must have survived the onset of the acute episode for at least 12 and preferably 24 hours. It is to be regretted that diffuse, circumferential, subendocardial necrosis is still classed by many observers (Baroldi *et al.*, 1974; Ehrlich and Shinohara, 1964) as myocardial infarction when its pathogenesis is different, though the two conditions, localized infarction and diffuse subendocardial or laminar necrosis, may coexist. In our series, the incidence of occlusive thrombi in diffuse subendocardial necrosis (13%) is very low, whereas the incidence of occlusive thrombi in localized infarction is high (95%), a fact emphasized by Miller, Burchell, and Edwards (1951) and Mitchell and Schwartz (1963). The severity of atherosclerosis as judged by the incidence of triple vessel disease is greater in subendocardial laminar necrosis, as is the incidence of healed infarction, indicating that severe diffuse coronary artery disease is the important predisposing factor. These findings suggest that this form of myocardial necrosis is the result of inadequate perfusion of the inner quarter of the myocardium of the left ventricle as a result of advanced, stenosing coronary atherosclerosis. In these cases there is a strong tendency to progressive dilatation of the left ventricle, the development of mitral regurgitation, and cardiac failure. An identical form of diffuse subendocardial necrosis is often seen in the hearts of patients who fail to survive cardiac bypass, when the coronary artery tree is anatomically normal but inadequately perfused at operation (Pomerance and Davies, 1975).

A second cause of confusion is the inclusion in other necropsy series of cases of sudden death attributable to coronary artery disease and thought to be the result of acute myocardial infarction (Spain and Bradess, 1960). The pathology of sudden cardiac death, at least in the United Kingdom, is still unknown largely because of the limits imposed on scientific investigation by the requirements of the coroner system. We believe, as do others (Friedman *et al.*, 1973; Liberthson *et al.*, 1974), that cases of sudden death from coronary artery disease can be subdivided into at least two groups, one consisting of patients with acute coronary occlusion in whom myocardial infarction could be anticipated had they survived long enough, and the other consisting of those with coronary artery disease who, for one reason or another, develop ventricular fibrillation but who would not necessarily have developed myocardial infarction had they survived. The relative size of the two groups is unknown and may be different in different places. It follows that when large numbers of cases of sudden death are included in series with the intention of investigating the pathology of myocardial infarction there will be a sharp drop in the incidence of coronary thromboses found at necropsy.

In our opinion localized myocardial infarction is the direct result of thrombotic occlusion of a major coronary artery, and in our series there was always a direct relation between the site of occlusion and the area of the infarct. Analysis of the small number of localized infarctions where no occlusion was found showed that in most of them there was severe calcification of the coronary arteries which had not been decalcified before dissection, making demonstration of thrombi difficult. Furthermore, even within our own department, there are significant differences between different prosectors in the proportion of patients with acute infarcts in which occlusive thrombi were found in the coronary arteries. We interpret this to indicate that the opinions of the prosector and the techniques employed in searching for thrombi must play a major role in producing the variability of reported results. In our series there is nothing to suggest that selection factors operate to influence results as necropsies were performed on a monthly roster system. We are not the first to suggest that the number of occlusive coronary thrombi found at necropsy is directly related to the care and energy expended in the search (Mitchell and Schwartz, 1963; Crawford, 1964; Chapman, 1974), and the interest and experience of the prosector.

Finally, the explanations invoked for infarction without occlusion leave much to be desired and pose more questions than they solve. If infarction does indeed cause coronary thrombosis, what is the explanation for those cases of sudden death, a not inconsiderable number, probably between 30 and 50 per cent, with coronary thrombosis but no infarct? Much of the argument in favour of the coronary thrombosis being a secondary result of stasis in the related artery following infarction is based on attempts to 'age' thrombi related to infarcts (Branwood and Montogomery, 1956; Baroldi, 1965). Ageing thrombi can be very difficult unless step serial sectioning is undertaken through the whole of the occlusion. A random section through a zone of propagated thrombus will be quite misleading when the original, older zone of occlusion has escaped observation. The further inability of pathologists to date accurately the duration of infarction makes any comparison of thrombus age to infarct duration 'doubly hazardous' (Burchell, 1974).

Incorporation of $^{125}$I into coronary thrombi after the onset of chest pain and electrocardiographic signs of infarction in living patients has been taken to prove that thrombosis follows infarction (Erhardt, Lundman, and Mellstedt, 1973). Two alternative explanations, however, exist: thrombi may propagate and thereby incorporate new fibrin; and labelled fibrinogen can diffuse into old thrombi. The confirmation of the latter finding in animal models (Kravis *et al.*, 1974) seriously questions the work of Erhardt and his colleagues (1973).

Careful histological examination of acute occlusions in coronary arteries indicates that plaque rupture commonly initiates thrombosis. This fact is clearly strong evidence against the suggestion that the thrombus is secondary to the infarct (Chapman, 1965; Bouch and Montgomery, 1970). It is of some interest that this finding has caused a change of view on the part of Montgomery, whose earlier paper (Branwood and Montgomery, 1956) is so often quoted by supporters of the view that thrombosis follows infarction. Finally, old canalized thrombi are a not infrequent finding in human coronary arteries without evidence of old myocardial infarction. It seems strange that Duguid's (Duguid, 1946) repeated assertion that mural thrombi are the major factor in plaque growth and the production of stenosis is now gaining general acceptance (Roberts, 1973), yet the same authors deny that thrombi are the final cause of occlusion. The occurrence of multiple old coronary occlusions in patients with recent infarction strongly suggests a generalized thrombotic tendency preceding the acute episode, and there is good evidence of long-standing episodic mural thrombi in the aortae of such patients (Woolf, Sacks, and Davies, 1969).

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# Congenital aortic valve disease with rupture of mitral chordae tendineae

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*A new clinical entity is described in which free aortic regurgitation from congenital aortic valve disease caused rupture of the chordae to the anterior leaflet of the mitral valve in 7 men aged 45 to 63 years (mean 52 years); 2 of the patients also had rupture of chordae to the posterior leaflet. Comparing these patients with those with ruptured mitral chordae in association with rheumatic heart disease and patients with spontaneous chordal rupture, differences were evident. No patient had a history of rheumatic fever and none had active infection. The typical clinical presentation was of acute mitral regurgitation into a small left atrium, with severe pulmonary oedema which was often resistant to medical treatment. The cause of chordal rupture in these patients was in part the result of progressive left ventricular dilatation, of direct trauma to the anterior cusp of the mitral valve, and possibly of a genetic factor. The anatomical features of both aortic and mitral valves are described, and in 3 histology of the mitral valve was available; 2 had myxomatous degeneration similar to that seen in patients with spontaneous chordal rupture, and in 1 there was degeneration of collagen tissue. All patients were treated surgically but the mortality was high (5 out of 7, 70%). Early operation with replacement of the aortic and mitral valves is recommended if this high mortality is to be reduced.*

Chordal rupture without obvious cause was described 40 years ago (Frothingham and Hass, 1934) but its importance has only become recognized relatively recently (Bailey and Hickam, 1944; Sanders *et al.,* 1965; Roberts, Braunwald, and Morrow, 1966; Klughaupt *et al.,* 1969; Eisenmann, 1973; Sutton, Chatterjee, and Caves, 1973). During the past decade, it has been recognized as a common cause of mitral regurgitation and is now believed to account for between 20 and 30 per cent of all cases of isolated mitral regurgitation (Ellis, Frye, and McGoon, 1966; Eisenmann, 1973). Previously rupture of mitral chordae was generally attributed to rheumatic heart disease with or without infective endocarditis (Osmundson, Callahan, and Edwards, 1958; Barrillon, Maurice, and Lenègre, 1967; Sanders *et al.,* 1967; Littler, Epstein, and Coulshed, 1973; Eisenmann, 1973).

Other causes of ruptured chordae include coronary artery disease, Marfan's disease, trauma, and the 'floppy valve syndrome' (Childress, Maroon, and Genovese, 1966; Barrillon *et al.,* 1967; Simpson, Nora, and McNamara, 1969; Bailey, Vera, and Hirose, 1969; Edwards, 1971; Cooley *et al.,* 1972; Eisenmann, 1973; Goodman, Kimbiris, and Linhart, 1974; Aranda *et al.,* 1975). Rare associations include pregnancy, left atrial myxoma, osteogenesis imperfecta, Ehlers-Danlos syndrome, gargoylism, acute rheumatic fever, scarlet fever, aneurysm of sinus of Valsalva, congestive cardiomyopathy, and hypertrophic cardiomyopathy (Frew, 1931; Wigle, 1964; Childress *et al.,* 1966; Barrillon *et al.,* 1967; Sanders *et al.,* 1967; Hwang and Lam, 1968; Soulié *et al.,* 1969; Sloman, Hunt, and Hare, 1969; Edwards, 1971; Caves and Paneth, 1972; Lainée *et al.,* 1972; Ghahramani *et al.,* 1972; Wood, Thomas, and Braimbridge, 1973; Wise, 1974).

This report describes 7 patients with severe aortic regurgitation caused by congenital aortic valve disease and ruptured mitral chordae tendineae, an association not previously reported. In these patients there was no history of rheumatic fever or evidence of rheumatic heart disease. One patient only had had infective endocarditis. In all patients, chordae to the anterior mitral cusp were involved and 6 of the 7 patients presented with acute heart failure.

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## Clinical data

The clinical details of the 7 patients are described. Haemodynamic data, and operative and pathological findings are summarized in the Table.

### Case 1

A man, known to have valvular heart disease since the age of 39 years, presented with acute left heart failure at the age of 62. There was no history of rheumatic fever. He had signs of severe aortic and mitral regurgitation, with clinical evidence of left and right ventricular hypertrophy and left heart failure. The chest radiograph showed pronounced cardiomegaly with pulmonary oedema and the electrocardiogram confirmed severe left ventricular hypertrophy and atrial fibrillation.

Emergency surgery without cardiac catheterization was undertaken. The aortic valve was calcified and bicuspid, with calcification in the rudimentary

TABLE *Clinical, haemodynamic, and pathological data*

| *Case No.* | *Sex* | *Age at opn* | *Cardiac rhythm* | *Duration of symptoms* | *Duration of final illness* | *Additional diagnosis* | *Haemodynamic data (mmHg)* | | | | | *Angiographic assessment* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *PCV mean* | *PCV 'v' wave* | *PA* | *PA mean* | *LV edp* | *AR* | *MR* |
| 1 | M | 62 | AF | 23 yrs | 3/12 | — | 24* | 55* | 55–60†/0* | 20* | — | — | — |
| 2 | M | 63 | SR | 7/12 | 7/12 | AVS | 20 | 35 | 55/12 | — | 20 | 2/4 | 2/4 |
| 3 | M | 50 | AF | 7/12 | 7/12 | CAD | 22 | 28 | 80/4 | 50 | 15 | 2/4 | 3/4 |
| 4 | M | 45 | SR | 18 yrs | — | — | — | — | — | — | — | 4/4 | — |
| | | 50 (second opn) | SR | | | | 12 | 18 | 34/6 | 18 | 9 | 2/4 | 3/4 |
| 5 | M | 45 | AF | 12 yrs | 9/12 | — | 18* | 27* | 42/17* | 27* | 25* | 2/4 | 2/4 |
| 6 | M | 51 | SR | 23 yrs | 1/12 | — | — | — | — | — | — | 2/4 | — |
| 7 | M | 47 | SR | 6 yrs | 4½/12 | — | 20 | 42 | 80/35 | 40 | 17 | 3/4 | 4/4 |

*Pressures obtained at operation.

†Right ventricular pressure.

*Abbreviations:* AF, atrial fibrillation: AML, anterior mitral leaflet; AR, aortic regurgitation; AVS, aortic valve stenosis; CAD, corona artery disease; LV edp, left ventricular end diastolic pressure; MR, mitral regurgitation; PA, pulmonary artery; PCV, pulmona capillary venous pressure; PML, posterior mitral leaflet; SR, sinus rhythm.

*Conversion from Traditional to SI Units:* 1 mmHg≈0·133 kPa.

commissure; the non-coronary cusp was shortened, allowing free regurgitation. The mitral valve annulus was very dilated; the anterior cusp was a little thickened and chordae to its centre were ruptured. The posterior cusp was normal and the chordae intact. Both valves were replaced with Starr-Edwards prostheses.

Initial progress was satisfactory but four months after operation he developed left heart failure and died at home.

| *Mitral valve* | | *Aortic valve* | |
|---|---|---|---|
| *Macroscopical appearance* | *Histology* | *Macroscopical appearance* | *histology* |
| AML—2 rupt. central chordae;<br>PML—normal;<br>annulus dilated | Myxomatous degeneration;<br>fibroelastic thickening | Bicuspid calcified | Myxomatous degeneration;<br>fibroelastic thickening |
| AML—3–4 rupt. ant-lat. chordae;<br>PML—normal;<br>annulus normal | Collagenous thickening and degeneration | Bicuspid calcified | Collagenous thickening, degeneration, and calcification |
| AML—rupt. ant-lat. chordae;<br>PML—voluminous;<br>annulus dilated | — | Bicuspid thickened | — |
| AML—2 rupt. chordae; voluminous;<br>PML—voluminous;<br>annulus dilated | — | Bicuspid calcified | Thickened and fibrosed |
| AML—same chordae rupt.;<br>voluminous;<br>PML—thickened;<br>voluminous;<br>annulus dilated | Myxomatous degeneration;<br>collagenous thickening and degeneration;<br>increased vascularity | — | — |
| AML—rupt. chordae at med. commissure;<br>PML—rupt. chordae at med. commissure;<br>annulus dilated | — | Bicuspid calcified | Nodular calcific fibrosis |
| AML—rupt. chordae to med. half;<br>PML—1 rupt. chorda;<br>annulus normal | — | Bicuspid calcified 'floppy' | — |
| AML—1 rupt. central chorda;<br>PML—normal;<br>annulus dilated | — | Bicuspid | — |

Histological examination of the aortic valve showed thickening of the valve leaflets caused by fibroelastic tissue with foci of calcification. Superimposed on the deformed face was a layer of collagen tissue, which suggested aortic regurgitation of some duration. Myxomatous degeneration was prominent. The mitral valve showed thickening of collagen tissue and extensive myxomatous degeneration in the centre of the anterior leaflet in the position of the zona spongiosa. Similar changes were present in the ruptured chordae. There was no increased vascularity.

## Case 2

A 63-year-old man with no rheumatic history presented with sudden onset of left heart failure, and effort angina. He had features of aortic valve disease with stenosis and regurgitation. On the chest radiograph there was considerable cardiomegaly with pulmonary venous congestion and aortic valve calcification, and electrocardiogram showed severe left ventricular hypertrophy. Cardiac catheterization confirmed aortic valve stenosis and regurgitation; and also showed important mitral regurgitation, without stenosis.

At operation the aortic valve was bicuspid and heavily calcified with a transverse opening. The chordae to the anterolateral part of the mitral anterior cusp were ruptured but the mitral valve was otherwise normal. Both valves were replaced with Starr-Edwards prostheses. The patient made an uncomplicated recovery apart from the onset of atrial fibrillation.

Microscopically the aortic valve leaflets were thickened, particularly towards the free edge. This thickening consisted of collagen tissue and foci of calcification. There was also some degeneration of the collagen tissue. Vascularity was not increased. The mitral valve showed uniform thickening caused by collagen tissue, which, particularly in the central portion of the valve leaflet, was associated with extensive degenerative changes; again the vascularity was not increased.

## Case 3

A 50-year-old man with no previous cardiac or rheumatic history presented with sudden onset of left heart failure. Clinically he had the signs of congestive cardiac failure, mitral regurgitation, and atrial fibrillation. Radiographic information is not available. Cardiac catheterization confirmed mitral regurgitation but aortography was not performed. He was discharged on medical treatment but 4 months later was readmitted with further cardiac failure and renal failure that later required haemodialysis. He was transferred to London 3 months later and at this time the chest radiograph showed considerable cardiomegaly. The electrocardiogram confirmed atrial fibrillation and left ventricular hypertrophy. A second cardiac catheterization confirmed severe mitral regurgitation, pronounced pulmonary hypertension, and important aortic regurgitation which had been suspected clinically. In view of the abrupt onset of symptoms the possibility of ruptured mitral chordae was considered.

At operation the aortic valve was bicuspid with a calcified rudimentary commissure, the cusps were thickened with rolled edges, and the valve was clearly regurgitant. The mitral annulus was very large; most chordae to the anterolateral end of the anterior cusp had ruptured allowing free mitral regurgitation. The posterior cusp was voluminous, but the chordae were intact. Both valves were replaced with Starr-Edwards prostheses.

Postoperative progress was uneventful but in spite of adequate anticoagulation he developed a cerebral embolism 14 months after operation, with transient dysphasia and hemiparesis. Two years later he suffered an anteroseptal myocardial infarction but made a satisfactory recovery.

Valve histology is not available.

## Case 4

A man aged 27 years without a history of rheumatic fever developed acute left ventricular failure. He was treated medically until the age of 37 years when he deteriorated and was admitted to hospital. Clinically he had severe aortic regurgitation which was confirmed by aortography. Surgery was advised but the patient declined. He was again treated medically but deteriorated progressively. At the age of 45 years when readmitted the chest radiograph showed considerable cardiomegaly, with pulmonary venous congestion, and electrocardiogram confirmed sinus rhythm with left atrial and severe left ventricular hypertrophy. In view of the earlier haemodynamic findings, a second cardiac catheterization was not performed.

At surgery the aortic valve was bicuspid, calcified, and grossly regurgitant. Severe mitral regurgitation was caused by 2 ruptured chordae to the anterior mitral cusp and the annulus was dilated. There was also a jet lesion on the anterior cusp of the mitral valve with shallow ulceration. A mitral annuloplasty was performed and the chordae were sutured; the aortic valve was replaced with a pulmonary autograft (Gonzalez-Lavin *et al.*, 1970a) and a pulmonary homograft was used to replace the pulmonary valve. He made a satisfactory recovery but he developed signs of mitral regurgitation 19 months later; at this time cardiac catheterization showed mild aortic regurgitation and moderate mitral regurgitation. He developed progressive symptoms but again refused surgery for a further 4 years when he was readmitted *in extremis*. At operation, which was undertaken as a matter of urgency, the anterior mitral leaflet was ballooned with thickening of the free margin. The repaired chordae of the anterior leaflet had ruptured and most of the unruptured chordae were slender though two, adjacent to the commissures, had thickened. The posterior leaflet was also thickened and ballooned into the left atrium but all the chordae were intact. There was moderate aortic regurgitation resulting from prolapse of one cusp of the pulmonary autograft, and a perforation of a second suggested previous infection. Degeneration of the pulmonary homograft had produced free pulmonary regurgitation. The pulmonary valve was replaced with an aortic homograft and the mitral and aortic valves with Starr-Edwards prostheses. The patient deteriorated because of infection of the homograft and died 2 weeks after the second operation from cardiac and renal failure.

Histology of the mitral valve showed uniform thickening and a prominent zona spongiosa with myxomatous degeneration, as well as degeneration of collagen tissue. The chordae showed similar changes. Both the degenerative areas gave a positive reaction with alcian blue stain. In the centre of the anterior mitral valve leaflet, thick-walled small vessels were identified. In view of the patient's previous operation, this increased vascularity could have been the result of the previous surgical intervention or, secondly, of inflammation such as infective endocarditis, but there was no history of this and no vegetations were seen. The pulmonary homograft showed some degenerative changes of collagen tissue and the body of the leaflet was totally devoid of nuclei, but the surfaces were covered with fibroblasts. One leaflet (anterior cusp) showed recent fibrin superimposition. There was no evidence of infection. The pulmonary autograft showed uniform thickening, together with mild degenerative changes of collagen tissue, and in these areas the nuclei were reduced. The leaflet in the position of the non-coronary cusp showed total destruction of normal architecture.

Pathology of the patient's original aortic valve is not available.

## Case 5

This man had no history of rheumatic fever, and heart disease was first diagnosed at the age of 33 years. He presented at the age of 42 years with moderate aortic regurgitation, having deteriorated with the onset of atrial fibrillation, but there was no other evidence of mitral valve disease. At the age of 44 he developed severe acute left ventricular failure with considerable cardiomegaly and the signs of aortic and mitral regurgitation. The electrocardiogram and chest radiograph confirmed severe left ventricular enlargement, and the diagnosis of aortic and mitral regurgitation was confirmed by angiography.

Surgery was initially refused but was undertaken as a matter of urgency 7 months later after a recurrence of heart failure with tricuspid regurgitation. The aortic valve was bicuspid with massive nodular calcification and fibrosis. It was replaced with a Starr-Edwards prosthesis. The mitral annulus was grossly enlarged with pliable cusps and ruptured chordae at the medial end of both anterior and posterior leaflets; an annuloplasty was performed with imbrication at the level of the ruptured chordae; the valve was subsequently competent. The tricuspid ring was also dilated and required an annuloplasty. After the operation severe neurological complications developed and he died 9 days later.

Histology of the mitral valve is not available.

### Case 6

A man developed breathlessness at the age of 37 years and had an attack of infective endocarditis at the age of 38 years when heart disease was first diagnosed. He had further attacks of infective endocarditis at 43 and 47 years. He presented at the age of 51 years with evidence of moderate aortic regurgitation, confirmed by aortography and slight mitral regurgitation. Chest radiograph at that time showed mild cardiomegaly with no evidence of left atrial enlargement, and electrocardiogram confirmed sinus rhythm with moderate left ventricular hypertrophy. He responded initially to medical treatment and was then lost to follow-up for 7 years. He returned at the age of 58 years; surgery was advised but he refused operation in spite of progressive symptoms.

Two years later at the age of 60 years he developed acute left ventricular failure. Chest radiograph showed further increase in heart size with pulmonary oedema, and electrocardiogram confirmed progressive left ventricular hypertrophy. Emergency surgery was undertaken without prior cardiac catheterization.

The aortic valve, which was congenitally bicuspid, was large and 'floppy'. There was minimal calcification, with prolapse of the non-coronary cusp. The mitral valve was grossly regurgitant because of rupture of the chordae from the medial half of the anterior cusp. In addition there was a single ruptured chorda from the posterior cusp. Both valves were replaced with Starr-Edwards prostheses. In spite of an adequate cardiac output immediately after the operation, his circulation deteriorated and he developed acute renal failure. Medical treatment, including peritoneal dialysis, failed to prevent his death on the fourth postoperative day.

Valve histology is not available.

### Case 7

A male patient had no rheumatic history but a cardiac murmur was heard during childhood. Aortic regurgitation was diagnosed at 41 years and he presented at the age of 44 years with sudden onset of left and right heart failure. He had signs of severe aortic and mitral regurgitation. The chest radiograph showed considerable cardiomegaly and pulmonary venous congestion, and an electrocardiogram confirmed left and right ventricular and left atrial hypertrophy. Angiography confirmed the diagnosis.

At surgery the aortic valve was bicuspid and uncalcified and the root large with a diameter of 3·3 cm; regurgitation was the result of cusp attenuation and insufficiency. The mitral ring was also grossly dilated with a diameter of about 8 cm; the valve cusps were thin and attenuated and one chorda to the central part of the anterior cusp was ruptured. Both valves were replaced with Starr-Edwards prostheses but the patient died from uncontrollable haemorrhage from the left coronary artery.

Valve histology is not available.

## Discussion

The clinical features of acute mitral regurgitation from ruptured chordae tendineae have been reviewed recently (Roberts and Perloff, 1972; Littler *et al.*, 1973; Sutton *et al.*, 1973). Some of the points which help to distinguish it from rheumatic mitral regurgitation with intact chordae are the short history, persistence of sinus rhythm, high left atrial pressure caused by a small non-compliant left atrium (Baxley *et al.*, 1973) and the unusual radiation of systolic murmurs. Before the syndrome became well recognized it was often mistaken for aortic stenosis because of the radiation of the mitral systolic murmur to the base of the heart (Osmundson *et al.*, 1958). This was particularly so when the chordae to the posterior mitral cusp were involved. When chordae to the anterior cusp were ruptured the radiation of the murmur was more typical of rheumatic mitral regurgitation. Some authors, however, have found that the radiation of the murmur was an unreliable guide to the nature of the regurgitation (Sutton *et al.*, 1973; Littler *et al.*, 1973). A further difficulty arises with the systolic ejection murmur which usually accompanies florid aortic regurgitation; this may mask the murmur of mitral regurgitation, especially when the latter is conducted to the base.

Ruptured chordae in association with rheumatic mitral and aortic valve disease with and without infective endocarditis is well recognized (Sanders *et al.,* 1967; Shine *et al.,* 1968; Gonzalez-Lavin, Lise, and Ross, 1970b). Other cases with aortic regurgitation have been recorded, but the nature of the valve lesions in these reports was not mentioned (Barrillon *et al.,* 1967; Manhas *et al.,* 1971). Rupture of mitral chordae associated with severe aortic regurgitation from a congenitally bicuspid aortic valve has not previously been reported.

Acute mitral regurgitation from chordal rupture frequently presents as unexpected left heart failure. This was so in 6 of our 7 patients. Four were in sinus rhythm and 4 had a small left atrium. As left heart failure in these cases was primarily mechanical, the result of ruptured chordae with subsequent prolapse of the anterior cusp and a dilated mitral annulus, it was not surprising that they failed to respond to medical treatment. In 6, surgery was undertaken within 7 months of the onset of symptoms. In spite of this, 4 were emergency procedures and the operative mortality was high; 5 out of the 7 (70%) died. If the mortality is to be reduced, the malignant course of mitral regurgitation from ruptured chordae must be recognized and surgery undertaken as soon as the diagnosis is made.

All 7 patients had bicuspid aortic valves; 6 were thickened and 4 were calcified. One valve was 'floppy' (Case 6) and aortic regurgitation in this case was caused by cusp prolapse. Histology was available on 4 of the aortic valves, one showed myxomatous degeneration (Case 1), while in another (Case 2) there were degenerative changes in the collagen tissue. In the remaining 2, non-specific fibrosis and calcification were found.

In 5 cases rupture of mitral chordae was confined to the anterior leaflet; in the remaining 2, chordae to both anterior and posterior cusps were involved. Five patients had considerable dilatation of the mitral annulus and in 2 there was excessive cusp tissue involving both leaflets in one and the posterior cusp in the other. There was no evidence in our patients that chordal rupture was caused by the more common aetiologies of rheumatic fever or infective endocarditis, except possibly in Case 6 where there was a history of bacterial endocarditis. In Case 4 the anterior leaflet of the mitral valve showed increased vascularity with thick walled vessels, which was thought to be caused by the previous mitral annuloplasty. Rheumatic endocarditis seemed unlikely as the normal architecture, though distorted by thickening, was not destroyed. Infective endocarditis also seemed improbable because of the absence of recent or healed vegetations. Histological examination of the 3 mitral valves available (Cases 1, 2, and 4) showed myxomatous degeneration together with degenerative changes in collagen tissue (Fig.), the latter being the only change seen in Case 2. The elastic tissue was often fragmented. These histological appearances were similar to those described in cases of spontaneous or idiopathic chordal rupture (Bailey and Hickam, 1944; Shine *et al.,* 1968; Gerbode *et al.,* 1969; Caulfield *et al.,* 1971; Caves, Sutton, and Paneth, 1973). Similar pathology is probably responsible for the floppy valve syndrome where from 9 to 20 per cent may develop ruptured chordae (Read, Thal, and Wendt, 1965; Pomerance, 1969; Cooley *et al.,* 1972). The 'floppy' or 'ballooning' mitral valve is probably responsible for the systolic click-late systolic murmur syndrome in which chordal rupture has also been reported (Goodman *et al.,* 1974).

The macroscopical appearances of the normal mitral valve have been described in detail by Ranganathan *et al.* (1970). The anterior leaflet consists of rough and clear zones, while the posterior leaflet, like the tricuspid valve, has an additional basal zone. On average 25 chordae are present, 9 are inserted into the anterior leaflet, the majority into the rough zone, while 14 usually form part of the posterior leaflet. The remaining 2 chordae are inserted at the commissures (Lam *et al.,* 1970). Basically the valve leaflets have two layers. The 'deformed' face which consists of elastic tissue, and the 'holding face' of collagen tissue. Not infrequently, an additional zone can be identified between these two layers, the so-called zona spongiosa (Gross and Kugel, 1931). When myxomatous degeneration is prominent, it is in a central position, so that it suggests an increase in the zona spongiosa. Frequently, however, degenerative changes in collagen tissue are also present. It may be that a prominent zona spongiosa is a genetically determined component which, in some cases, degenerates in later life, giving rise to the 'floppy valve' syndrome.

Caulfield *et al.* (1971) considered myxomatous degeneration to be enzymatic destruction of normal collagenous and elastic structure. The same authors noted the presence of blood vessels in normal chordae but reported fewer in degenerated zones. There is increasing evidence that ischaemia, which is known to cause papillary muscle dysfunction and rupture, is also a factor in chordal rupture (Sanders *et al.,* 1967; Barrillon *et al.,* 1967; Gerbode

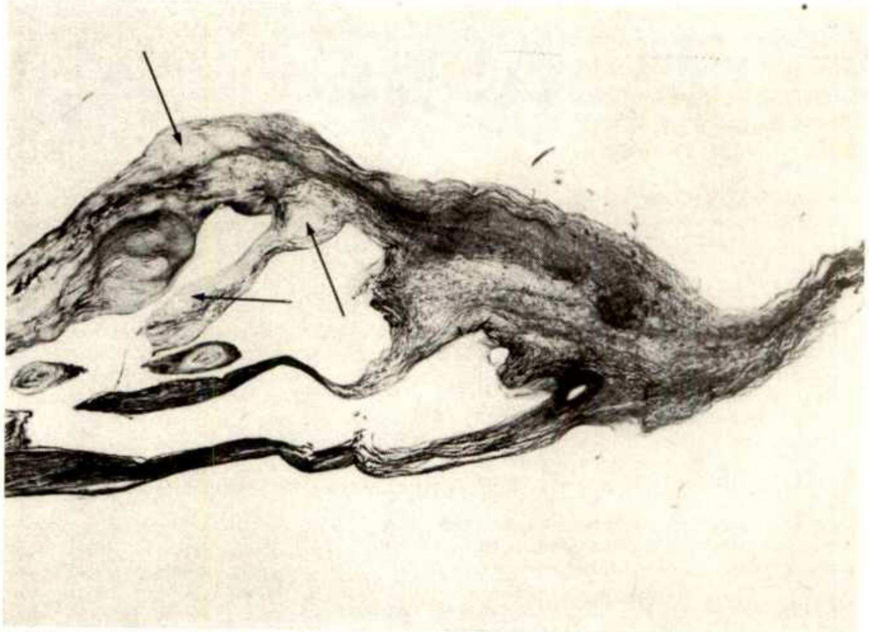

FIG. *Photomicrograph (Weigert's elastic van Gieson. ×12) from Case 4 showing distal portion of the anterior mitral leaflet and severed chordae. Areas of myxomatous degeneration in both the valve leaflet and chordae are marked with arrows.*

*et al.,* 1968; Klughaupt *et al.,* 1969; Eisenmann, 1973; Caves *et al.,* 1973; Aranda *et al.,* 1975). It is generally agreed that in the physiological state it is the chordae to the anterior leaflet which are subjected to the greater stress (Chiechi, Lees, and Thompson, 1956). So it is somewhat surprising that in cases of spontaneous chordae rupture (i.e. without other obvious pathology) it is usually the posterior mitral leaflet that is affected (Sanders *et al.,* 1965; Marchand *et al.,* 1966; Raftery, Oakley, and Goodwin, 1966; Acar *et al.,* 1968; Selzer *et al.,* 1972). In the normal valve mechanical stress on the mitral chordae during ventricular systole is probably not great. Marchand *et al.* (1966) when repairing ruptured chordae, noted little tension on nylon threads used when they were exteriorized through the left ventricular wall. Similar views were expressed by Salisbury, Cross, and Rieben (1963) who found that stress borne by normal mitral chordae diminished after aortic valve opening and before the development of peak systolic pressure. Furthermore, rupture of normal chordae is not particularly common in conditions such as aortic stenosis where peak left ventricular pressure may be abnormally high.

Pre-existing abnormalities of the left ventricle and the mitral valve almost certainly increase chordal stress. Edwards and Burchell (1958) postulated that left ventricular dilatation from whatever cause altered the normal lie of chordae, in which they are parallel to the inflow tract, thus increasing the stress to which they were subjected. Aortic regurgitation not only has this effect by increasing the diastolic volume, but the regurgitant jet may impinge directly onto the anterior cusp of the mitral valve causing local trauma to the valve leaflet and chordae (Gonzalez-Lavin *et al.,* 1970b). This probably explains why, in the presence of aortic regurgitation, it is usually the chordae to the anterior cusp of the mitral valve which are ruptured (Menges, Ankeney, and Hellerstein, 1964; Ellis *et al.,* 1966; Littler *et al.,* 1973; Eisemann, 1973). In addition, Shine *et al.* (1968) suggested that the rapid recoil of the left ventricle in early diastole contributed to the mechanical stress to which the chordae of the anterior mitral leaflet were subjected. In the 7 patients reported here all factors for increasing chordal stress were present; in addition there may have been a congenital fault in the mitral valve tissue.

We consider that this syndrome is a new clinical entity in which free aortic regurgitation from congenital aortic valve disease causes progressive left ventricular dilatation and direct trauma to the anterior cusp of the mitral valve. These factors combine, generally without infection, and lead to rupture of the chordae to the anterior leaflet. The classical picture is of acute mitral regurgitation into a small left atrium, with severe pulmonary oedema which is often resistant to medical treatment. Early surgical treatment with replacement of aortic and mitral valve is indicated.

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# Endocardial cushion defects
## *An anatomical study of 54 specimens*

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*An anatomical study of 54 specimens with endocardial cushion defect is described. The material was divided into two groups, according to the morphology and attachments of the anterior component of the anteroseptal mitral leaflet.*

*We suggest that there is no divided or undivided anterior common leaflet. There are always two anterior leaflets, a mitral and a tricuspid one, separated by a commissure; depending on the degree of straddling of the mitral component over the interventricular septum, this will protrude into the interventricular septum or into the anterior papillary muscle of the right ventricle. Thus, the commissure separating the mitral and the tricuspid components will lie over the interventricular septum or will be quite separate in the right ventricle. In the latter case the straddling mitral component gives the false appearance of an undivided anterior common leaflet.*

*The septal tricuspid leaflet was found to be underdeveloped or absent but we were not able to find any clefts or divisions in it. We suggest that this leaflet derives solely from the division of the posteroinferior endocardial cushion into two halves, right and left. The left half later becomes the posterior component of the normal anteroseptal mitral leaflet.*

*Associated anomalies are also reviewed.*

Endocardial cushion defects form a wide spectrum of anomalies (Campbell and Missen, 1957; Kiely *et al.*, 1958; Neufeld *et al.*, 1961; Al Omeri *et al.*, 1965), ranging from the isolated left axis deviation of the QRS (Sumner *et al.*, 1967) to the so-called persistent common atrioventricular canal in its complete form.

The endocardial cushions are responsible for the development of the posterior smooth septum (Wakai and Edwards, 1956, 1958; Van Mierop *et al.*, 1962; Goor, Edwards, and Lillehei, 1970a; Goor *et al.*, 1970b), the membranous septum (Campbell and Missen, 1957; Van Mierop *et al.*, 1962; Odgers, 1938), the anteroseptal mitral leaflet (Grant, 1962), the septal and posterior tricuspid leaflets (Al Omeri *et al.*, 1965; Van Mierop, 1969; Grant, 1962), and indirectly for the correct anatomical distribution of the conduction system (Feldt, DuShane, and Titus, 1970). The part they play in the development of the anterior tricuspid leaflet and the posterior ventricular wall has not been clearly explained.

Stimulated by recent papers (Goor, Lillehei, and Edwards, 1968; Tenckhoff and Stamm, 1973; Blieden *et al.*, 1974), we examined our necropsy material with special reference to the anatomy of the atrioventricular valves, their relation to the interventricular septum, and the haemodynamic, angiocardiographic, and surgical implications.

## Patients and methods

A study was made of 54 necropsy specimens from the anatomical collection of the Clínica Infantil 'La Paz', Madrid, which showed endocardial cushion defect. Cases with important dominance of a ventricle and/or total or partial absence of the subvalvular apparatus in the underdeveloped ventricle were excluded (single ventricle and related anomalies).

We accept the embryological origin of the atrioventricular valves as shown in Fig. 1.

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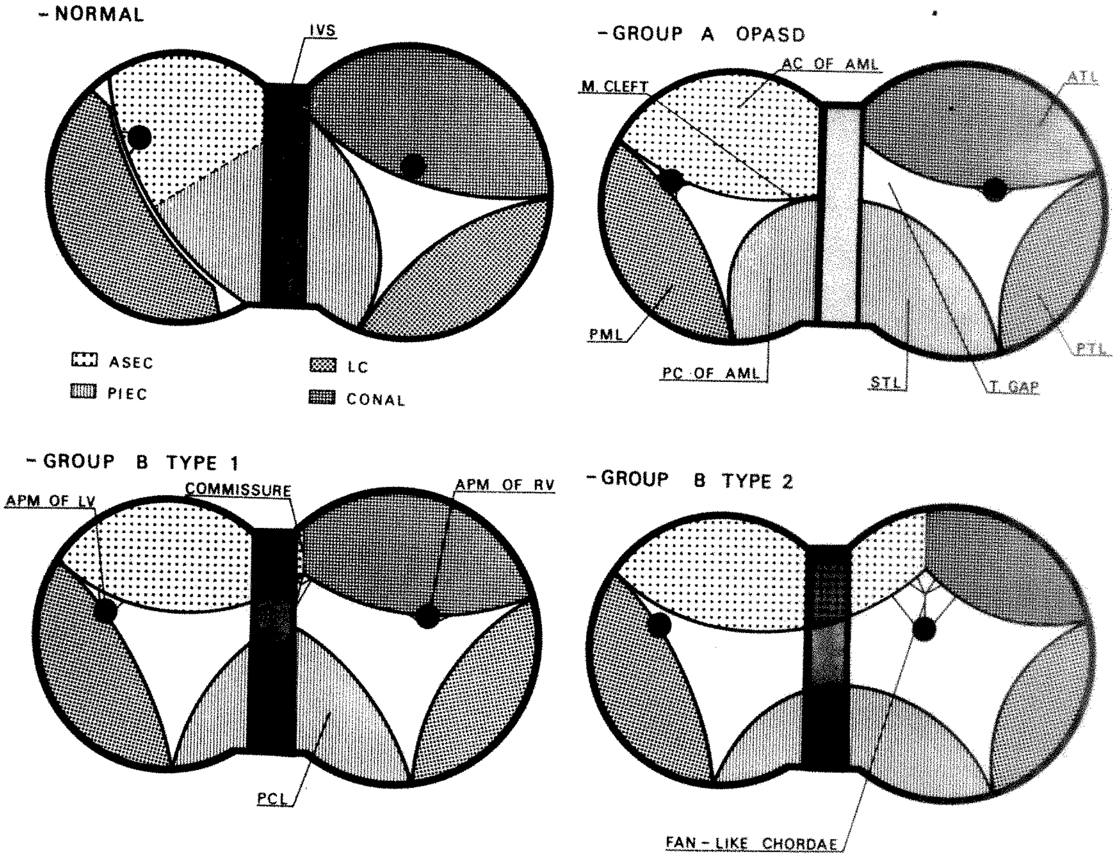

FIG. 1 *Diagrammatic representation of anatomical components of atrioventricular valves in normal heart and in different types of endocardial cushion defect.*

Upper left: *normal heart. Anterosuperior endocardial cushion (ASEC) converts wholly into anterior component of anteroseptal mitral leaflet (AC of AML). Posteroinferior endocardial cushion (PIEC) converts into posterior component of anteroseptal mitral leaflet (PC of AML) and septal tricuspid leaflet (STL). Posterior mitral leaflet (PML) and posterior tricuspid leaflet (PTL) are developed from left and right lateral cushions (LC), respectively. Anterior tricuspid leaflet (ATL) is considered to be of conal origin.*

Upper right: *Group A: ostium primum atrial septal defect (OPASD). Existence of fibrous continuity between AC of AML and PC of AML, though cleft is present between them (M. cleft). STL is smaller than usual and there is gap (T. gap) between it and ATL, where normal anterior tricuspid commissure should be.*

Lower left: *Group B: type 1. AC of AML joins ATL forming commissure which is attached by short chordae tendineae to crest of interventricular septum (IVS). Mediallly-located fissure tending to divide posterior common leaflet (PCL) into two halves.*

Lower right: *Group B: type 2. Commissure between AC of AML and ATL is inserted into anterior papillary muscle of right ventricle (APM of RV) and is located more to right than in cases of type 1 because of straddling of AC of AML over IVS towards right ventricle and to smaller-sized ATL. APM of RV in these cases may be located more medially than usual.*

*In all three types of endocardial cushion defects anterior papillary muscle of left ventricle (APM of LV) is usually laterally displaced with respect to normal heart.*

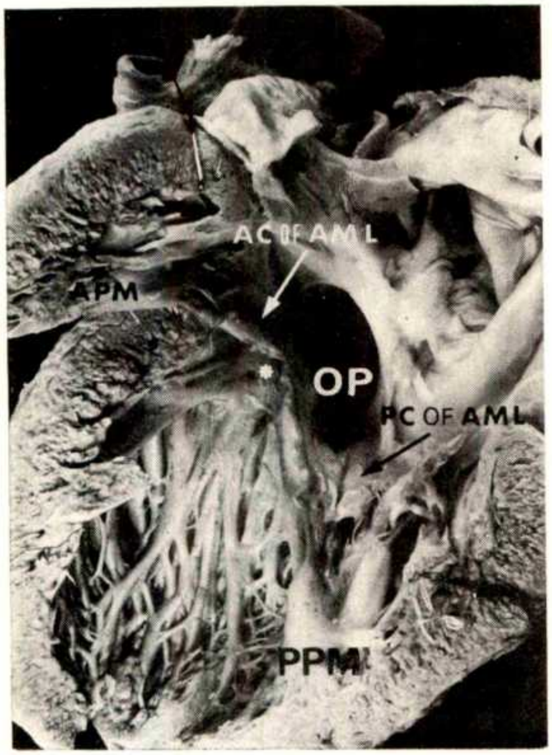

FIG. 2 *Left ventricular view of group A case. Ostium primum (OP) and cleft (*) between anterior (AC of AML) and posterior (PC of AML) components of anteroseptal mitral leaflet. Upward displacement of anterior papillary muscle (APM) and increased mass of posterior group of papillary muscles (PPM).*

The following elements have been examined in the atrioventricular valves.

### (A) Anterior component of anteroseptal mitral leaflet

### (B) Posterior common leaflet

This represents the incomplete development of the posteroinferior endocardial cushion and its subsequent failure to divide into the posterior component of the anteroseptal mitral leaflet and the septal tricuspid leaflet, where this exists (Van Mierop, 1969; Grant, 1962).

### (C) Left and right lateral leaflets

The left lateral leaflet later becomes the posterior mitral leaflet in cases of ostium primum atrial septal defect and in normal hearts, while the right one becomes the posterior tricuspid leaflet (Al Omeri *et al.*, 1965; Van Mierop, 1969).

### (D) Anterior tricuspid leaflet

This is generally thought to be partially or totally of conal origin (Odgers, 1938; Al Omeri *et al.*, 1965; Van Mierop, 1969; Tenckhoff and Stamm, 1973).

Previously reported criteria (Lam *et al.*, 1970; Ranganathan *et al.*, 1970; Silver *et al.*, 1971) for the identification of the commissures in normal hearts were used.

Our material has been classified as follows.

### Group A (7 cases)

This group includes those specimens showing two well-differentiated atrioventricular valves with fibrous continuity between the anterosuperior endocardial cushion and the posteroinferior endocardial cushion, or, in other words, between the anterior and posterior components of the anteroseptal mitral leaflet. Those are the cases usually known as

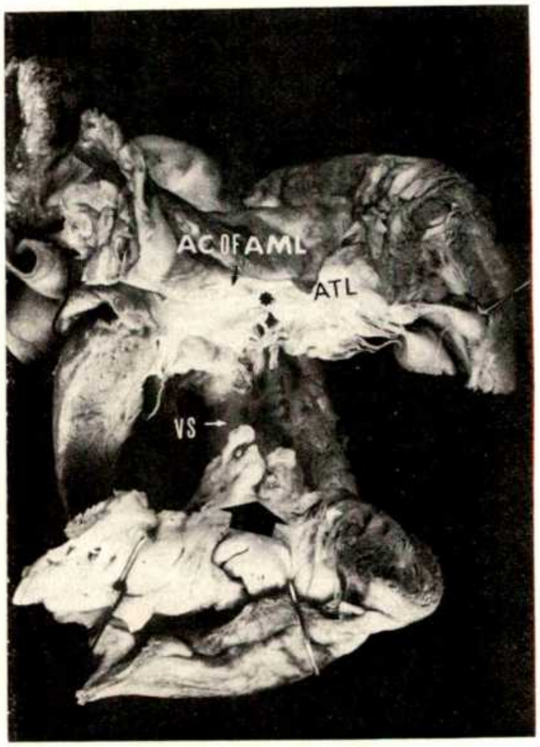

FIG. 3 *Group B type 1 case, viewed from above. Commissure (*) between anterior component of anteroseptal mitral leaflet (AC of AML) and anterior tricuspid leaflet (ATL) is inserted by means of short chordae tendineae into top rim of interventricular septum (VS). Fissure (arrow) in posterior common leaflet (PCL) divides it into two halves of roughly similar size.*

ostium primum atrial septal defect (Fig. 1, upper right, and Fig. 2), and we include here the partial and transitional forms of Wakai and Edwards (1956, 1958).

### Group B (47 cases)

This group includes those specimens showing discontinuity between the anterosuperior endocardial cushion and the posteroinferior endocardial cushion, being the so-called persistent common atrioventricular canal in the complete form of Wakai and Edwards. This group consists of two types.

**Type 1** (26 cases) Here the anterior component of the anterior mitral leaflet attaches on its medial side to the interventricular septum and is not connected to the anterior papillary muscle of the right ventricle (Fig. 1, lower left, and Fig. 3).

**Type 2** (21 cases) Here the anterior component of the anteroseptal mitral leaflet straddles the interventricular septum and inserts into the anterior papillary muscle of the right ventricle (Fig. 1, lower right, and Fig. 4).

We analysed the insertions of the anterior and posterior leaflets into the interventricular septum and the nature of these insertions when found. We also dealt with the ventricular septal defects under the leaflets, the presence of redundant valvular tissue, the number, position, and size of the papillary muscles, and the presence of accessory valvular orifices, identified as such by the presence of chordae tendineae inserted into the annulus of the orifice.

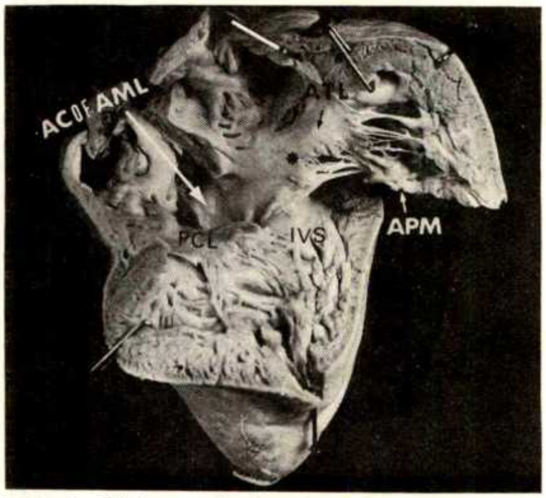

FIG. 4 *Right ventricular view of group B type 2 case. Commissure (*) between straddling anterior component of anteroseptal mitral leaflet (AC of AML) and anterior tricuspid leaflet (ATL) is displaced far towards right, being clearly contained in right ventricle and anchored by means of 'fan-like' chordae to anterior papillary muscle (APM). PCL = posterior common leaflet. IVS = interventricular septum.*

An analysis of the atrial septum was included. The septum primum was considered to be intact when at its anterosuperior and posteroinferior limits, it joined the base of the atrioventricular valves and there was no important defect above an imaginary line joining both limits.

The anatomy of the interventricular septum was studied according to recent papers by Goor *et al.* (1970a, b).

We tried to recognize the septal and moderator bands whenever it was possible to do so with reasonable certainty.

The out-flow/in-flow tract ratio was measured (Goor *et al.*, 1968; Tenckhoff *et al.*, 1973; Blieden *et al.*, 1974). Atrial straddling of the interventricular septum (Tenckhoff and Stamm, 1973; Yokoyama *et al.*, 1973) and ventricular dominances (Bharati and Lev, 1973) were also investigated.

The associated anomalies were recorded, and special attention paid to those of truncoconal nature.

## Results

### Atrioventricular valves

In 45 cases of group B a commissure was identified between the anterior component of the anteroseptal mitral leaflet and the anteroseptal tricuspid leaflet.

This commissure does not exist in normal hearts, since in these the anteroseptal tricuspid leaflet, at its medial commissure, joins the septal tricuspid leaflet. In two other group B type 2 cases this commissure was not identified in one case, because of deterioration of the region and, in the other, because of hypoplasia of the anteroseptal tricuspid leaflet. In one group B type 1 case and three group B type 2 cases there was partial fusion of the anterior component of the anteroseptal mitral leaflet and the anteroseptal tricuspid leaflet; a clear fusion line was identified. In group A the anterior component of the anteroseptal mitral leaflet, instead of being connected to the anteroseptal tricuspid leaflet, joined the posterior component of the anteroseptal mitral leaflet, derived from the posteroinferior endocardial cushion. A cleft between the two components was always present (Fig. 2).

A ventricular septal defect under the anterior component of the anteroseptal mitral leaflet and the posterior common leaflet has been frequently found in every group (Table 1), even in group A. A

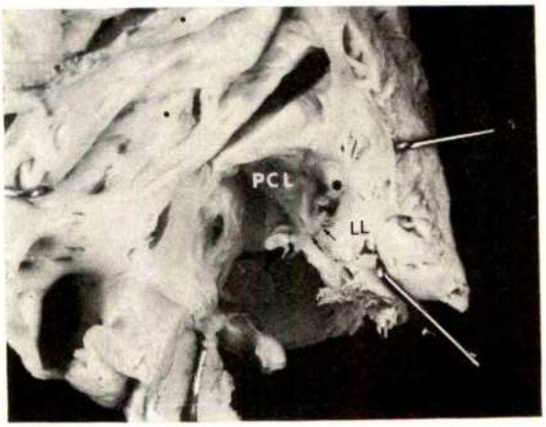

FIG. 5 *Left atrial view of group B type 2 case showing accessory atrioventricular orifice (*). Fusion line (arrows) between posterior common leaflet (PCL) and left lateral leaflet (LL).*

medially-located fissure in the posterior common leaflet was present in 17 cases (36%) in group B (Fig. 3), partially dividing this leaflet into right and left halves. This fissure was more common in group B type 1 cases (42%). Redundant valvular tissue has also been frequently encountered in this leaflet.

Twenty-four accessory valvular orifices were found in our material, evenly distributed in all groups. All but a few were on the fusion line of two valvular leaflets, usually between the lateral and the posterior, sometimes between the lateral and the anterior, and even, on occasion, between the anterior mitral and tricuspid leaflets. Usually the fusion line was easily recognizable (Fig. 5).

### Papillary muscles

Position anomalies of the papillary muscles were encountered mainly in the left ventricle, and usually consisted of a lateralization and upwards displacement of both papillary muscles. This anomaly occurred in all cases of group A and in 27 group B cases, and was more frequent in type 1 of group B (17 cases, 65%) than in type 2 (group B) (10 cases, 48%). In 6 cases (29%) of type 2 (group B) a medial displacement of the anterior papillary muscle of the right ventricle was seen.

TABLE 1 *Number and location of ventricular septal defects*

| *Group* | *VSD under AC of AML* | *VSD under PC of AML* |
|---|---|---|
| A | 2 (29%) | 1 (14%) |
| B–1 | 23 (88%) | 19 (73%) |
| B–2 | 21 (100%) | 16 (76%) |

VSD, ventricular septal defect; AC of AML, anterior component of anteroseptal mitral leaflet; PC of AML, posterior component of anteroseptal mitral leaflet.

The papillary muscle of the conus was absent in 19 cases (91%) of type 2 (group B). By contrast, this structure was found to exist in 31 cases (94%) of the remaining specimens not included in type 2 (group B).

One case in group A showed parachute atrioventricular valve in both ventricles; the overall incidence of parachute atrioventricular valves in our material was 9·3 per cent. Accessory papillary muscles were often found, usually lateral and in some cases were large.

### Atrial septum

After careful evaluation, the septum primum was considered intact in 5 cases (71%) of group A, 16 cases (62%) of type 1 (group B) and in 11 cases (52%) of type 2 (group B). An ostium secundum atrial septal defect was present in 48 per cent of all

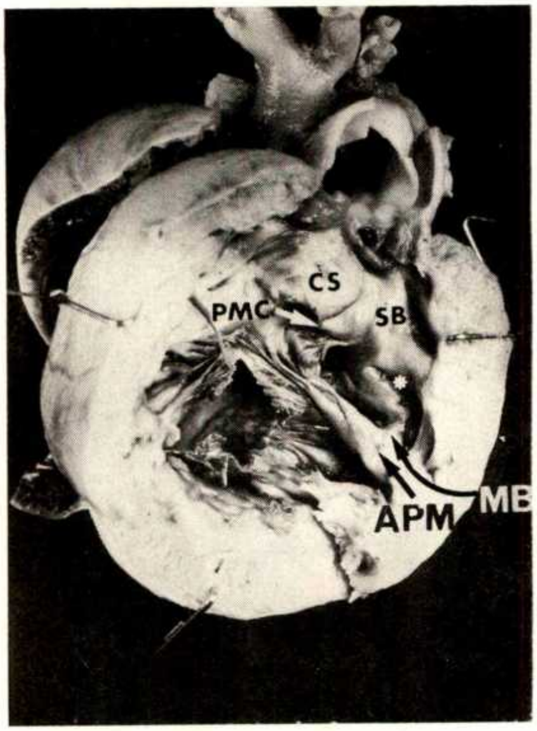

FIG. 6 *Right ventricular view of group B type 1 case. Bifid nature (*) of inferior extremity of septal band (SB). CS = conal septum. MB = moderator band. PMC = papillary muscle of conus. APM = anterior papillary muscle of right ventricle.*

TABLE 2 *Percentage of deficiency of left ventricular posterior wall according to out-flow/in-flow tract ratio*

| *Group* | *Per cent deficiency (±SD)* |
|---|---|
| A | 24·7±7·7 |
| B–1 | 27·9±8·8 |
| B–2 | 23·6±8·1 |

cases. Five cases of type 1 (group B), and another five of type 2 (group B) presented a single atrium. No instance of single atrium was found in group A.

### Interventricular septum

Membranous septum was deficient or absent in every case in group B, whereas it was present in all the cases in group A. Anterior smooth septum was deficient in 9 cases (19%) of group B, there being no difference between types 1 and 2. No case among those studied showed a defect in the trabeculated septum. Posterior smooth septum was naturally deficient in all cases.

### Septal and moderator bands

It was not possible to recognize the septal band in one case of group A, 8 cases (31%) of type 1 (group B), and 5 cases (24%) of type 2 (group B). In addition, 3 cases of group A, 9 cases of type 1 (group B), and 7 cases of type 2 (group B) showed a bifid inferior division of the septal band. The anterior division pointed towards the apex of the right ventricle and the posterior one formed the moderator band (Fig. 6).

### Out-flow/in-flow tract ratio in left ventricle

The posterior wall of the left ventricle was in all cases undersized The degree of underdevelopment of the left ventricular posterior wall was similar in all groups (Table 2).

### Atrial straddling and ventricular dominances

In one case in group A, 11 cases of type 1 (group B) and 10 cases of type 2 (group B) the right atrium straddled the interventricular septum and the atrial septum lay to the left, leaving a smaller than normal left atrium in those cases.

TABLE 3 *Major associated anomalies*

| *Type* | *TGV* | *PAA* | *TF* | *IPS* | *Asplenias* |
|---|---|---|---|---|---|
| Group B, 1 | 2 | 1 | 1 | 1 | 2 |
| Group B, 2 | — | 1 | 3 | — | — |

TGV, transposition of great vessels; PAA, pulmonary artery atresia; TF, tetralogy of Fallot; IPS, infundibular pulmonary stenosis.

*Note:* Only Group B is shown, as there was no instance of major associated anomalies in group A.

A right or left ventricular dominance was encountered in some cases. There was no instance of left ventricular dominance in group A, the right ventricle being dominant in 4 cases in this group. In group B ventricular dominances were evenly distributed.

### Associated malformations

Major associated anomalies are described in detail in Table 3. Truncoconal malformations were found only in group B, occurring as frequently in type 1 as in type 2. There were no associated major malformations.

There was a high incidence of persistent ductus arteriosus in all groups. Minor associated anomalies included one case of coarctation of the aorta, 7 cases of aortic arch anomalies, and 8 cases of persistent left superior vena cava draining either to the coronary sinus (7 cases) or to the left atrium (1 case). In addition, one case of type 1 (group B) showed a partial anomalous pulmonary venous drainage

Four cases in group A, 9 cases of type 1 (group B), and 6 cases of type 2 (group B) showed no associated malformation.

## Discussion

Endocardial cushion defects have, in the past, been classified in a variety of ways (Campbell and Missen, 1957; Wakai and Edwards, 1956, 1958; Rastelli, Kirklin, and Titus, 1966; Rastelli *et al.*,

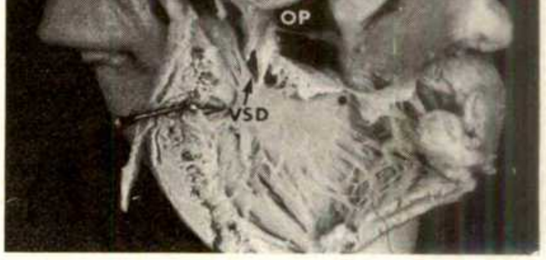

FIG. 7 *Left ventricular view of group A case. Anterior component of anteroseptal mitral leaflet (AC of AML) is attached to crest of interventricular septum by short chordae tendineae which leave multiple ventricular septal defects (VSD) between them. OP=ostium primum; (*)=cleft of the anteroseptal mitral leaflet.*

1968; Quero *et al.*, 1974) in accordance with the various criteria applied. Classifications have usually been based upon the morphology and attachments of the so-called anterior common leaflet, though the anatomically less anomalous cases (ostium primum atrial septal defect) have always been considered separately. The most widely accepted classification is that proposed by Rastelli and co-workers (1966, 1968); some aspects of it, however, have recently been questioned (Tenckhoff and Stamm, 1973; Quero *et al.*, 1974), especially type II. Thus, endocardial cushion defects are at present divided into two types—always with the exception of ostium primum atrial septal defect—according to the presence or absence of attachments between the so-called anterior common leaflet and the interventricular septum.

A review of our necropsy material according to the embryological scheme previously outlined in this paper showed that in group B cases the valvular apparatus was always composed of two elements on its anterior side—a left or mitral one and a right or tricuspid one, separated by a commissure. The component situated to the right of the commissure is always an anteroseptal tricuspid leaflet whose size may vary. The component situated to the left of the commissure—the mitral component—may insert on its medial side into the anterior papillary muscle of the right ventricle (group B, type 2 cases) or into the interventricular septum (group B, type 1 cases), while on its lateral side it always inserts into the anterior papillary muscle of the left ventricle.

Early in the life of the embryo the anterosuperior endocardial cushion is found straddling the interventricular septum; it later rotates and shifts towards the left ventricle to become the anterior component of the anteroseptal mitral leaflet (Grant, 1962) and fuses to its posterior component developed from the posteroinferior endocardial cushion. If the anterior component of the anteroseptal mitral leaflet is displaced towards the left ventricle, as in the normal heart, but is only partially fused to the posterior component, a cleft in the anteroseptal mitral leaflet will result (group A, ostium primum atrial septal defect). If the anterior component of the anteroseptal mitral leaflet is shifted towards the left ventricle but has not fused to the posterior component, its medial side will insert into the crest of the interventricular septum and the commissure separating it from the anteroseptal tricuspid leaflet will necessarily be located over the interventricular septum (group B type 1). If the anterior component of the anteroseptal mitral leaflet is not shifted towards the left ventricle nor has fused to the posterior component developed from the posteroinferior endocardial cushion, it will insert on its medial side into the anterior papillary muscle of the right ventricle, thus giving the false appearance of an anterior common leaflet. Nevertheless careful inspection will reveal that, to the right of this anterior component, and separated from it by a commissure, there exists an anteroseptal tricuspid leaflet, however small. In such cases this commissure will be located in the right ventricle (group B type 2).

The underdevelopment of the anteroseptal tricuspid leaflet in some of these cases may be the result of the fact that, since the anterosuperior endocardial cushion is abnormally located, the anteroseptal tricuspid leaflet cannot so easily develop from the dextrodorsal conus swelling and a lesser amount of endocardial tissue of conal origin is able to reach the atrioventricular ring.

In some of our cases of type 2 (group B) it seemed at first sight that there was no anteroseptal tricuspid leaflet. It did, however, exist, and was located in its normal place, though on the anterior side of the mitral component that straddled the interventricular septum, and was hidden by it. It seems that an anteroseptal tricuspid leaflet had developed from the dextrodorsal conus swelling, even though ousted from its normal location by the abnormally sited anterosuperior endocardial cushion. The final result was something like a double or overlapping leaflet in the anterior tricuspid region.

Thus, we consider that the concept of a divided or undivided anterior common leaflet (Rastelli *et al.*, 1966, 1968) must be re-examined and that we should think in terms of an anterior component of the mitral leaflet attached to the interventricular septum or a straddling anterior component of the anteroseptal mitral leaflet anchored to the anterior papillary muscle of the right ventricle. The division usually described in the anterior common leaflet is a commissure between the anterior component of the anteroseptal mitral leaflet, originally the anterosuperior endocardial cushion, and an anterior tricuspid component of conal origin. In support of this we adduce the presence of 'fan-like' chordae, previously reported as commissure markers in normal hearts (Lam *et al.*, 1970; Ranganathan *et al.*, 1970; Silver *et al.*, 1971), which we found in the majority of our type 2 (group B) cases (Fig. 4).

A fissured posterior common leaflet (Fig. 3) is found more frequently in type 1 (group B) cases than in type 2 (group B), and, in our opinion, indicates a more advanced stage of development, since such fissures are the first indication of the posterior common leaflet dividing to produce the posterior component of the anteroseptal mitral leaflet and the septal tricuspid leaflet.

A cleft septal tricuspid leaflet was not found in our study, a fact that seems to favour the idea that it is developed from the posteroinferior endocardial cushion and does not have a dual origin, as some authors have suggested (Wakai and Edwards, 1956, 1958; Kiely *et al.*, 1958; Al Omeri *et al.*, 1965; Tenckhoff and Stamm, 1973).

The presence of significant ventricular septal defects under the anterior and posterior leaflets in cases of group A (Fig. 7), and the fact that the posterior smooth septum is consistently deficient (Goor *et al.*, 1968), in our opinion qualifies these cases where they occur to be included under the general heading of persistent common antrioventricular canal. In our classification we include them as 'cases with fibrous continuity between both endocardial cushions', and we consider them as a group which shows the same basic malformation.

The very frequent presence of significant ventricular septal defects under both anterior and posterior leaflets in group B cases, even in those attaching medially to the interventricular septum, needs further emphasis. These ventricular septal defects allow shunts to occur, and are difficult to identify, since at present there are no satisfactory haemodynamic or angiocardiographic criteria by which they may be identified (Baron *et al.*, 1964; Wakai, Swan, and Wood, 1956; Cornell, 1965; Rastelli, Kirklin, and Kincaid, 1967; Somerville and Jefferson, 1968; Gotsman, Beck, and Schrire, 1968). Furthermore, they may prevent successful conservative surgery if residual shunts are present (Vanetti and Daumet, 1975).

The accessory valvular orifices, as previously reported (Campbell and Missen, 1957), were mainly located at the fusion line of two leaflets; in many of them the cicatricial fusion line was clearly visible (Fig. 5).

Anomalies of papillary muscles have been described previously (Al Omeri *et al.*, 1965; Tenckhoff and Stamm, 1973; Bharati and Lev, 1973). There are three striking features about the cases studied: firstly, in the left ventricle, the papillary muscles tended to lateralize and fuse, which perhaps explains the high incidence of parachute atrioventricular valves in this malformation. Secondly, the frequent medial deviation of the anterior papillary muscle of the right ventricle in type 2 (group B) cases (Rastelli *et al.*, 1966, 1968) may be because this muscle is connected to a valvular component from the left ventricle. Thirdly, the high percentage of positional anomalies of the papillary muscles of the left ventricle in group A cases (100% in our material) could prevent normal functioning of the mitral valve after conservative surgery (Frater, 1965; Somerville, 1966).

The septum primum could be considered intact in a great percentage of cases. This leads us to believe, with other authors (Wakai *et al.*, 1956; Wakai and Edwards, 1958; Kiely *et al.*, 1958; Baron *et al.*, 1964; Al Omeri *et al.*, 1965; Frater, 1965; Quero *et al.*, 1974) that the septum primum plays no part in the complex of malformations, and that the ostium primum atrial septal defect is actually a result of insufficient upwards growth of the endocardial cushions. Moreover, some cases have been reported (Neufeld *et al.*, 1961; Goor *et al.*, 1968; Quero *et al.*, 1974) of endocardial cushion defects without ostium primum atrial septal defect in which the anomalies were limited to the atrioventricular valves and the interventricular septum.

Septal and moderator bands were difficult to recognize in a great number of cases. Also worthy of note is the frequency with which a bifid inferior division was present on the septal band (Fig. 6). This phenomenon needs further study, as the embryological origin of these structures is still not completely explained.

In agreement with results obtained by previous authors (Goor *et al.*, 1968; Tenckhoff and Stamm, 1973; Blieden *et al.*, 1974), we have consistently found a shortening of the posterior wall of the left ventricle, as measured by the out-flow/in-flow tract ratio in the left ventricle. In some of our cases, however, the electrocardiogram showed right axis deviation of the QRS even where a pronounced shortening of the left ventricular posterior wall occurred.

Deviation of the atrial septum was a common finding (Tenckhoff and Stamm, 1973; Yokoyama *et al.*, 1973); the right atrium straddled the interventricular septum, suggesting that in some cases cyanosis may coexist with normal pressures on the pulmonary trunk (Campbell and Missen, 1957; Tenckhoff and Stamm, 1973; Quero *et al.*, 1974).

Among associated malformations, the commonest was persistent ductus arteriosus; the poorer prognosis of any left-to-right shunt associated with persistent ductus arteriosus may explain the high incidence of this malformation in necropsy material.

Group A did not show the associated severe anomalies occurring in the rest of the specimens. Truncoconal malformations were concentrated in group B, but occurred as frequently in type 1 as in type 2. This agrees only partially with the findings of previous authors (Rastelli *et al.*, 1966, 1968; Bharati and Lev, 1973; Tenckhoff and Stamm, 1973), a discrepancy which we have been unable to explain.

Consequently, we consider that endocardial cushion defects are a continuous spectrum of malformations the anatomy of which depends on the horizon on which the growth of the posteroinferior endocardial cushion is stopped and the degree of displacement of the anterosuperior endocardial cushion towards the right ventricle. Further haemodynamic and angiocardiographic findings are needed to reach a precise preoperative diagnosis. The surgeon who operates upon an endocardial cushion defect must be prepared to cope with the different types of the malformation, and avoid any type of intervention that might worsen the haemodynamic status of the malformation (Frater, 1965; Somerville, 1966).

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# Influence of heart rate increase on uncorrected pre-ejection period/left ventricular ejection time (PEP/LVET) ratio in normal individuals

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*In 26 normal volunteers, increase in heart rate from mean $73{\cdot}94 \pm 1{\cdot}97$ to $103{\cdot}61 \pm 2{\cdot}72$/min, by either intravenous atropine administration or rapid right atrial pacing, produced definite changes in the uncorrected systolic time intervals. As expected, total electromechanical systole ($QS_2$) and left ventricular ejection time (LVET) were shortened, while the pre-ejection period (PEP) was unaffected. There was a consistent and significant increase of the PEP/LVET ratio ($P<0{\cdot}001$). It is postulated that when this ratio is taken to express left ventricular contractility, it should probably be corrected for heart rate. Appropriate regression equations for such a correction were calculated ($PEP/LVET=0{\cdot}249-0{\cdot}0168\ HR$).*

Measurement of the systolic time intervals of the left ventricle as reported by Weissler, Harris, and Schoenfeld (1968, 1969) is currently being applied widely for the evaluation of cardiac function. The advantages and reliability of this method, as well as reservations about its validity, have been already discussed in numerous publications (Aronow, Bowyer, and Kaplan, 1971; McConahay, Martin, and Cheitlin, 1972; Parker and Just, 1974). Weissler and co-workers (1969) have particularly stressed the use of the pre-ejection period/left ventricular ejection time (PEP/LVET) ratio as a very sensitive index of ventricular function. According to these investigators this ratio offers the additional advantage of being self-corrected for sex and heart rates from 50 to 110/min. Most authors have subsequently adhered to this principle, and have used the PEP/LVET ratio in its uncorrected form (McConahay *et al.*, 1972; Timmis *et al.*, 1975). However, it becomes apparent from Weissler's own regression equations and additional investigators' reports that the PEP and the external isovolumic contraction time (EICT) are only minimally affected by changes in heart rate (Goldstein, DeGroot, and Leonard, 1961; Harris, Schoenfeld, and Weissler, 1967; Talley, Meyer, and McNay, 1971), while the LVET is altered to a considerable degree (Wallace *et al.*, 1963). Therefore, changes in heart rate would be expected to yield a larger PEP/LVET ratio.

We investigated whether correction of this ratio for heart rate is justified. Some authors have already corrected this ratio, using Weissler's equations (Strangfeld *et al.*, 1973; Frishman *et al.* 1975), but as far as we know no detailed data have been given on the behaviour of this ratio with heart rate changes.

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## Subjects and methods

Twenty-six subjects were included in this study. Most were house physicians, and hospital personnel. In two patients STI intervals were measured during the process of rapid right atrial pacing for the investigation of atypical chest pain (both tests proved negative). Ages ranged from 17 to 38 years (mean 27·1). All were considered free from any cardiac abnormality by history, clinical examination, resting and exercise electrocardiograms (submaximal test: 85% of predicted maximal heart rate), and evaluation of heart size and motion by image intensifier fluoroscopy. The electrocardiogram (usually lead II), carotid pulse tracing, and phonocardiogram were recorded on a Hewlett-Packard 4578A photographic multichannel recorder. Thus, the heart rate, total electromechanical systole ($QS_2$), and left ventricular ejection time (LVET) were

TABLE *Systolic time intervals before and after the production of tachycardia*

| *Case No.* | *Sex* | *Age (y)** | *I: Basal* *HR min* | *$QS_2$ (ms)* | *LVET (ms)* | *PEP (ms)* | *PEP/ LVET* | *$PEP_I$/ $LVET_I$* | *II: After tachycardia* *HR min* | *$QS_2$ (ms)* | *LVET (ms)* | *PEP (ms)* | *PEP/ LVET* | *$PEP_I$/ LVET* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 21 | 61 2 | 416·0 | 303 8 | 112·2 | 0·369 | 0 340 | 92·3 | 381·0 | 265 3 | 115 7 | 0·436 | 0 369 |
| 2 | M | 36 | 56·5 | 452 4 | 347 5 | 104 9 | 0 301 | 0·287 | 63·4 | 445 1 | 338·1 | 107·0 | 0 316 | 0·296 |
| 3 | F | 20 | 81·0 | 388·3 | 276·5 | 111 8 | 0·404 | 0·355 | 127 6 | 331·5 | 224·8 | 106 7 | 0·474 | 0·367 |
| 4 | F | 20 | 79·0 | 381·4 | 283·0 | 94 8 | 0·334 | 0 308 | 130 1 | 331 1 | 239 1 | 92 0 | 0 384 | 0·322 |
| 5 | M | 25 | 83·9 | 374·5 | 266·0 | 108 5 | 0·407 | 0·347 | 107 3 | 324·5 | 224 0 | 100 5 | 0 448 | 0 352 |
| 6 | M | 19 | 59 5 | 415·3 | 307·5 | 107 8 | 0·350 | 0 322 | 96 8 | 340 0 | 243·5 | 96·5 | 0 396 | 0·331 |
| 7 | M | 17 | 72·4 | 381·2 | 281 7 | 99·5 | 0 353 | 0·317 | 113 2 | 341·5 | 231·1 | 110·4 | 0 477 | 0 367 |
| 8 | M | 24 | 62 5 | 365 6 | 276 7 | 88·9 | 0 321 | 0·297 | 96·7 | 344·2 | 260 0 | 84·2 | 0·323 | 0 289 |
| 9 | A | 22 | 77·1 | 397·7 | 287·7 | 110 0 | 0·382 | 0 342 | 107 1 | 373 9 | 249 7 | 124·2 | 0 497 | 0·386 |
| 10 | A | 22 | 71 2 | 417·5 | 301 4 | 116·1 | 0·385 | 0·342 | 93·0 | 384 5 | 262·8 | 121 7 | 0·463 | 0 377 |
| 11 | A | 37 | 82 9 | 379 0 | 275·3 | 103 7 | 0 376 | 0·335 | 109 0 | 338·8 | 232·6 | 106 2 | 0·456 | 0·368 |
| 12 | F | 38 | 68 7 | 391 4 | 276 5 | 114 9 | 0 415 | 0·361 | 107 1 | 324 2 | 219·0 | 105 2 | 0 480 | 0·379 |
| 13 | F | 23 | 75·3 | 387·8 | 287·8 | 100·5 | 0·349 | 0 319 | 87·3 | 380 7 | 285 0 | 95 1 | 0 332 | 0·306 |
| 14 | F | 24 | 70 6 | 385 4 | 278 7 | 106 7 | 0·382 | 0·344 | 103·6 | 365·0 | 263·0 | 102 0 | 0 387 | 0·334 |
| 15 | M | 38 | 77 0 | 388 5 | 284·5 | 104 0 | 0 365 | 0·324 | 114·7 | 324·0 | 229 5 | 94·5 | 0·411 | 0·411 |
| 16 | F | 30 | 91 0 | 411 4 | 316·0 | 95·4 | 0·301 | 0 285 | 109·0 | 379·1 | 286·2 | 92·9 | 0 324 | 0·296 |
| 17 | F | 22 | 82·6 | 393·3 | 298·2 | 95 1 | 0 318 | 0 297 | 104·7 | 348 1 | 263 8 | 84·3 | 0·319 | 0·292 |
| 18 | F | 29 | 66 6 | 432·0 | 317·3 | 114·7 | 0 361 | 0 333 | 105·2 | 374·5 | 257 2 | 117·3 | 0 456 | 0 374 |
| 19 | M | 17 | 88·0 | 358·6 | 252·4 | 104 2 | 0·412 | 0·346 | 124·2 | 321·7 | 214·2 | 107 5 | 0·501 | 0·369 |
| 20 | M | 30 | 69 3 | 424 2 | 297 0 | 127·2 | 0·428 | 0·373 | 86·2 | 410·0 | 278·5 | 132 0 | 0 473 | 0 391 |
| 21 | M | 31 | 80 3 | 373·4 | 272·8 | 100 6 | 0·368 | 0 328 | 101 6 | 358·1 | 256·1 | 102 0 | 0·398 | 0·332 |
| 22 | M | 30 | 79 1 | 395 8 | 277·0 | 118 8 | 0 428 | 0·365 | 93·7 | 386·3 | 256 5 | 129 8 | 0·506 | 0 402 |
| 23 | M | 30 | 64 2 | 418·5 | 308·3 | 110·2 | 0·357 | 0 325 | 100·0 | 364·5 | 246·0 | 118 5 | 0·481 | 0·385 |
| 24 | M (P) | 30 | 93 7 | 361 5 | 259·5 | 102 0 | 0·393 | 0 333 | 111 1 | 344 0 | 243·3 | 100·7 | 0·414 | 0·335 |
| 25 | M | 34 | 67·7 | 418·5 | 298·7 | 119 8 | 0·401 | 0 354 | 100·0 | 371·4 | 243 0 | 128 4 | 0·528 | 0·407 |
| 26 | M (P) | 38 | 61·2 | 413 5 | 299 4 | 114 1 | 0·381 | 0 343 | 109·0 | 348·6 | 245·7 | 102·9 | 0 418 | 0·339 |
| Mean | | 27 1 | 73·94 | 397·0 | 289·66 | 107·16 | 0 370 | 0·331 | 103 61 | 359·08 | 252·23 | 106·85 | 0·426 | 0·349 |
| SEM | | | ±1 97 | ±2 72 | ±3 99 | ±1·75 | ±0 0071 | ±0 0047 | ±2·72 | ±5·79 | ±5·09 | ±3 26 | ±0·0143 | ±0·007 |
| | | | | (548·29) | (412·41) | (136 73) | | | | (572 71) | (424·23) | (148 28) | | |
| | | | | ±3 20 | ±3 09 | ±1·61 | | | | ±3·2 | ±2·84 | ±2 56 | | |
| Significance | | | | | | | | | | | | | | |

*Abbreviations:* HR: Heart rate; (P): right atrial pacing.
In parentheses: Corrected values for heart rate according to Weissler's regression equations.

calculated, as proposed by Weissler *et al.* (1968, 1969). The PEP was estimated by subtracting the LVET from the $QS_2$. All measurements were performed between 8·00 and 9·00 a.m. at the fasting state and supine position.

Paper speed was 100 mm/s. Ten to fifteen consecutive heart beats were measured to the closest 5 ms and averaged. Care was taken to start and finish measuring at the same respiratory phase, as estimated by direct observation of the patient and manual marking of the inspiration phase on the chart paper. The arterial blood pressure was measured by a cuff sphygmomanometer immediately after recording the systolic time intervals.

The nature and purpose of this study was explained to all participants and informed consent was obtained.

After the initial basal study, atropine was given intravenously in 0·5 mg increments every 3 minutes to 24 subjects, until a heart rate around 110/min or a total dose of 1·5 mg was reached. The systolic time intervals were measured at the highest rate achieved. In 2 subjects, in whom rapid right atrial pacing was performed, they were measured at basal heart rate levels and at 111·1 and 109·0 beats/min, 2 minutes after these heart rates had been reached (Table).

Before and after the production of tachycardia, the $QS_2$ index ($QS_{2I}$), PEP index ($PEP_I$), and LVET index ($LVET_I$) were calculated according to the regression equations of Weissler *et al.* (1969)

Males:
$QS_{2I} = QS_2 + 2{\cdot}1$ heart rate
$LVET_I = LVET + 1{\cdot}7$ heart rate
$PEP_I = PEP + 0{\cdot}4$ heart rate

Females:
$QS_{2I} = QS_2 + 2{\cdot}0$ heart rate
$LVET_I = LVET + 1{\cdot}6$ heart rate
$PEP_I = PEP + 0{\cdot}4$ heart rate

| *ΔHR* | *ΔPEP/ LVET* | *$\Delta PEP_I/LVET_I$* | *% PEP/ LVET* | *% $PEP_I/LVET_I$* | *Δ%* |
|---|---|---|---|---|---|
| 31·1 | +0·067 | +0·029 | +18·15 | + 8·52 | 9·62 |
| 6·9 | +0·015 | −0·099 | + 4·98 | −3·13 | 8.11 |
| 46·6 | +0·070 | +0·012 | +17·32 | + 3·38 | 13·93 |
| 51·1 | +0·050 | +0·014 | +14·97 | + 4·54 | 10·42 |
| 23·4 | +0·041 | +0·005 | +10·07 | + 1·44 | 8·62 |
| 37·3 | +0·046 | +0·014 | +13·14 | + 4·34 | 8·79 |
| 40·8 | +0·060 | +0·050 | +16·99 | +15·77 | 1·21 |
| 34·2 | +0·002 | −0·008 | + 0·62 | − 2·69 | 3·31 |
| 30·0 | +0·155 | +0·044 | +40·57 | +12·86 | 27·7 |
| 21·8 | +0·078 | +0·035 | +20·25 | +10·23 | 10·02 |
| 26·1 | +0·080 | +0·033 | +21·28 | + 9·85 | 11·43 |
| 38·4 | +0·065 | +0·018 | +15·66 | + 4·98 | 10·68 |
| 12·0 | −0·017 | −0·013 | − 4·78 | − 4·07 | 0·80 |
| 33·0 | +0·005 | −0·010 | + 1·30 | − 2·90 | 4·20 |
| 37·7 | +0·046 | +0·006 | +12·60 | + 1·85 | 10·75 |
| 18·0 | +0·023 | +0·011 | + 7·64 | + 3·86 | 3·78 |
| 22·1 | +0·001 | −0·005 | + 0·31 | − 1·68 | 1·99 |
| 38·6 | +0·095 | +0·041 | +26·31 | +12·31 | 14·00 |
| 36·2 | +0·044 | +0·023 | +10·67 | + 6·64 | 4·03 |
| 16·0 | +0·045 | +0·018 | +10·51 | + 4·82 | 5·69 |
| 21·3 | +0·030 | +0·004 | + 8·15 | + 1·22 | 6·93 |
| 14·6 | +0·078 | +0·037 | +18·22 | +10·14 | 8·08 |
| 35·8 | +0·124 | +0·025 | +34·73 | + 7·69 | 27·04 |
| 17·4 | +0·021 | +0·002 | + 5·34 | + 0·60 | 4·74 |
| 32·3 | +0·127 | +0·053 | +31·67 | +14·97 | 16·7 |
| 47·8 | +0·037 | −0·004 | + 9·71 | + 1·17 | 10·88 |
| 29·66<br>±2·27 | 0·054<br>±0·0078 | 0·016<br>±0·0038 | +14·08 | + 4·78 | 9·36<br>±1·24 |
|  | P<0·001 | P<0·001 |  |  | P<0·001 |

After the PEP/LVET ratio was calculated, a $PEP_I/LVET_I$ ratio was also estimated. The values of both ratios before and after the production of tachycardia were compared by the paired t test.

The PEP/LVET and the $PEP_I/LVET_I$ ratio were correlated to heart rate either before the production of tachycardia (26 correlations), or after its production (26 correlations). Moreover, these ratios were correlated with heart rate both at rest and at tachycardia (52 correlations), by the regression analysis test.

## Results

Under basal conditions the systolic time interval values in our subjects were within the accepted normal range (Table). With increase of the basal heart rate from 73·94±1·97 to 103·61±2·72/min, there was a consistent shortening of the $QS_2$ and LVET, while the PEP did not appreciably change. The PEP/LVET ratio increased consistently and significantly (Table, Fig. 1). The $PEP_I/LVET_I$ was also found to increase with heart rate. However, the percentage change in each patient was significantly smaller in the $PEP_I/LVET_I$ ratio than in the PEP/LVET ratio ($P<0·001$, Table).

The PEP/LVET or the $PEP_I/LVET_I$ ratio in the 26 subjects were not related to heart rate at rest ($r=0·168$; $P>0·10$, and $r=0·0143$, $P>0·10$, respectively). They were not significantly related to the heart rate after tachycardia, either ($r=0·336$, $P>0·05$ and $r=0·102$, $P>0·10$, respectively). However, when all 52 heart rate measurements (before and after tachycardia) were pooled the PEP/LVET ratio was significantly correlated to heart rate ($r0=·508$, $P<0·01$, Fig. 2).

When the $PEP_I/LVET_I$ ratio was used, there was no correlation of the 52 measurements to heart rate ($r=0·267$, $P>0·05$, Fig. 3).

From the correlation of PEP/LVET to the total of 52 heart rate measurements the following regression equation was calculated:

PEP/LVET: 0·249+0·00168 HR.

The arterial blood pressure was normal in all subjects, and did not appreciably change with the increase in heart rate.

## Discussion

From our findings we cannot reach any conclusions as to whether the PEP/LVET should always be corrected for heart rate or not. However, we are puzzled by certain discrepancies in the published reports. It has been shown that the PEP is only minimally affected by changes in the heart rate (Harris *et al.*, 1967; Talley *et al.*, 1971); our findings are similar.

The PEP is significantly correlated with dP/dt max and the ejection fraction (Aronow *et al.*, 1971, McConahay *et al.*, 1972; Ahmed *et al.*, 1972); a weaker but still quite satisfactory correlation has also been found with the stroke volume (Weissler *et al.*, 1968, 1969; Ahmed *et al.*, 1972).

The stroke volume is affected considerably by tachycardia (Weissler, Peeler, and Roehll, 1961; Stein *et al.*, 1966; Benchimol and Liggett, 1966). It is probable that the PEP is prevented from lengthening during the tachycardia-induced decrease in stroke volume by a compensatory shortening through the increased contractility associated with tachycardia (Vatner and Braunwald, 1974; Schwarz, Thormann, and Winkler, 1975; Roy, Sowton, and DiLuzio, 1975).

The ejection fraction does not significantly change with tachycardia in dogs (Bristow *et al.*,

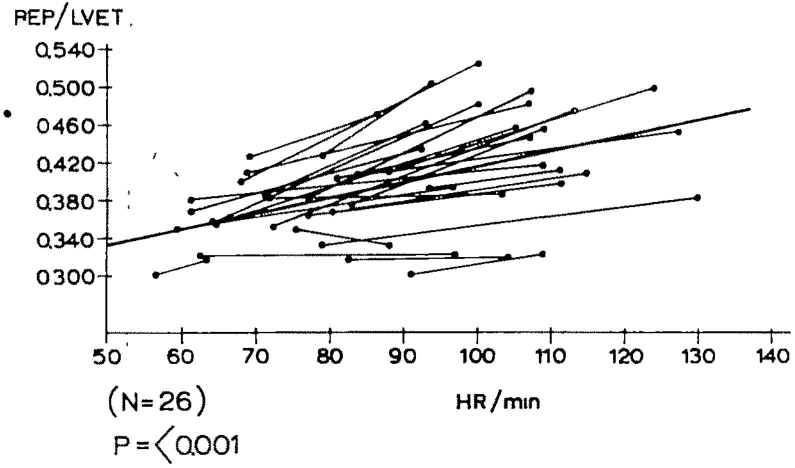

FIG. 1 *Increase of the uncorrected PEP/LVET ratio over the basal values with the occurrence tachycardia in the 26 patients used in the present study.*

1963) or humans (Krayenbuehl *et al.*, 1975).

There is agreement among the various authors about the profound effects of heart rate changes on the LVET. When rate corrected, this interval correlates well with the stroke volume and ejection fraction, but less well with the dP/dt (McConahay *et al.*, 1972).

The uncorrected PEP/LVET (and its reverse analogue, the LVET/EICT) ratio has been found to correlate better with the ejection fraction and dP/dt than the corrected LVET, PEP, or EICT alone (Garrard, Weissler, and Dodge, 1970; Aronow *et al.*, 1971; McConahay *et al.*, 1972). If this ratio is used as an expression of stroke volume, then it should probably not be rate-corrected. However, if it is taken as an index of cardiac contractility, or the ejection fraction, it should be rate-corrected, especially when serial measurements are carried out in the same individual after pharmacological or physiological interventions. Otherwise, any drug or man-

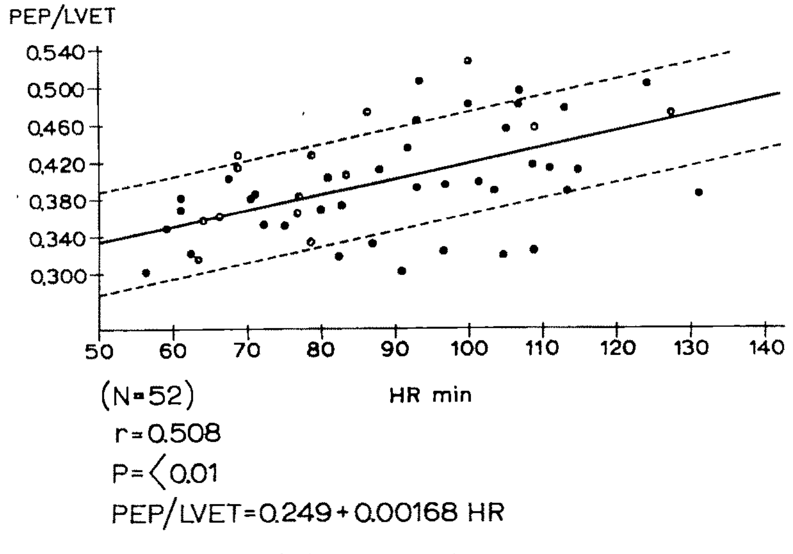

FIG. 2 *Significant correlation of the uncorrected PEP/LVET ratio with 52 heart rate measurements (26 patients, studied at basal conditions and after production of tachycardia).*

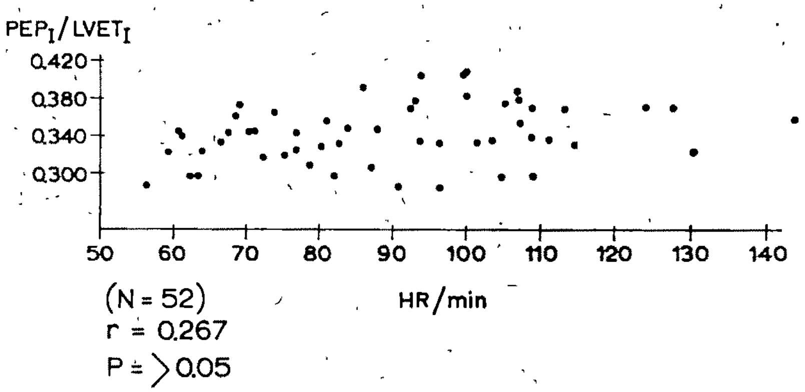

FIG. 3 *Absence of correlation of the* $PEP_I/LVET_I$ *ratio with 52 heart rate measurements. Correction of both PEP and LVET has been carried out according to Weissler's regression equations.*

oeuvre affecting increases in the HR can increase the uncorrected PEP/LVET ratio; thus a diminution of left ventricular contractility may be mistakenly suggested. Spitaels *et al.* (1974) have recently found that in normal children there is no correlation between the PEP/LVET and heart rate found under basal conditions. Our data are in complete accord with this finding. Probably, PEP/LVET values differ so much among individual patients, that the influence of heart rate does not become apparent when an individual is studied at random. Thus, in Fig. 2 it can be seen that the ratio PEP/LVET would be 0·410 at a heart rate of 70/min, and 0·380 at a heart rate of 110/min and still lie within the confidence limits, since there is a large scatter of values. However, when large groups of subjects are compared, or when the inotropic action of various interventions which also significantly affect heart rate is assessed in groups or individuals, or when single patients are studied serially, then rate correction should probably be carried out.

We do not know whether the regression equations that we propose are realistic enough. Probably individual correction for each subject would have been preferable, but our recordings of STI at intermediate heart rates during atropine infusion were too few to allow such a calculation.

We noticed that if we corrected the PEP/LVET ratio for the observed heart rate changes by simply substituting for it the $PEP_I/LVET_I$ ratio, according to Weissler's equations, there was still an increase of this ratio with tachycardia, as compared with the basal state (Table).

Up to the rates attained in our subjects, even this correction may still erroneously underestimate contractility.

Weissler's equations and those of Fabian, Epstein, and Coulshed (1972) were calculated from studies performed on a group of 121 men and 90 women with normal cardiac function, under basal conditions. Thus, these equations may not be appropriate for correcting the STI in serially studied individuals. On the other hand, Layton *et al.* (1973) and Lindquist, Spangler, and Blount (1973) used regression equations based on serial measurements.

In most of our subjects tachycardia was produced by atropine. This drug has been widely used to this purpose by Weissler's group (Harris *et al.*, 1967), who consider it free of any inotropic action. Similarly, Kosowsky *et al.* (1966) found no differences in the haemodynamic measurements between atropine and right atrial pacing-induced tachycardia.

We have no haemodynamic or angiographic studies to support our findings. However, such studies have been carried out in detail by others, as already discussed, and there is no reason why these data should not apply for the individuals presented in our report. It is self-evident that these conclusions are valid as long as tachycardia does not produce ischaemia, which would alter both the haemodynamic parameters and the systolic time interval values.

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# Plasma urea in hypertensive patients

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*The annual increase in plasma urea was measured in 253 hypertensive patients. On average there was a significant increase in plasma urea with time which did not depend on the sex of the patient or the type of hypertension. It did, however, depend on the initial level of plasma urea. A table giving the upper limits for expected annual increment may prove useful in clinical assessment.*

*The relation between plasma urea and presenting blood pressure and age was examined in 1217 patients seen at the Hammersmith Hospital hypertension clinic from 1952 to 1967. The plasma urea was significantly related to both age and diastolic and systolic blood pressure. It was higher in men than in women up to 60 years of age, but not above that age, and it increased with presenting mean blood pressure in both sexes, but the increase was greater in men. There was a quadratic relation between age and plasma urea in both men and women. In both sexes the plasma urea increased between the ages of 60 and 80.*

A pathological lesion in a kidney may increase blood pressure by several mechanisms; conversely in essential hypertension the kidneys may be morphologically normal but renal function may be impaired. It is generally accepted that hypertension itself can damage the renal microvasculature and up to a third of treated hypertensives who die may die from renal failure (Breckenridge, Dollery, and Parry, 1970). There has been no reduction in deaths from hypertensive renal disease in the United Kingdom (Registrar General, 1973), but the mortality from both hypertensive heart failure and malignant hypertension has been falling.

For these reasons the clinician is interested in the factors influencing renal function in the hypertensive patient. Long-term assessment of renal function in a hypertensive patient usually relies on repeated measurements of plasma urea or creatinine. This paper examines the plasma urea concentrations in hypertensive patients seen at a clinic and the annual increment in plasma urea during follow-up. By considering confidence limits for these increases a clinician may assess the change in renal function of his patients.

The annual increment in plasma urea does not correlate well with blood pressure control during treatment (Bulpitt, 1974), and this article examines the relation between plasma urea before treatment and the patient's presenting blood pressure, age, and sex.

## Patients and methods

### Patients studied

**Group 1** The case records were examined of all patients attending the Hammersmith Hospital hypertension clinic during a three-month period between November 1970 and January 1971. Of these patients 253 who had attended for at least 5 years and had had at least 4 measurements of plasma urea were selected. The information recorded included sex, age, diagnosis, hypotensive treatment given, and plasma urea measurements with dates. Any in-hospital measurements after a surgical operation were omitted.

Of the 253 patients, 77 had been diagnosed as having hypertension which might be 'secondary' to a renal lesion; 23 of these patients had chronic pyelonephritis, 6 renal calculi, 6 renal artery stenosis, 10 only a single kidney, and the remainder a variety of renal lesions. Their average follow-up was 7 years during which a mean of 12 plasma urea estimations were made.

**Group 2** The relation between the pretreatment blood pressure and the plasma urea on presentation

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TABLE 1 *Average plasma urea (mmol/l) and annual increment (mmol/l per year) according to the type of hypertension and sex for group 1*

| *Measurement* | *Men* | | | *Women* | | | |
|---|---|---|---|---|---|---|---|
| | *Essential hypertension* | *'Secondary' hypertension* | *Significance of between-diagnoses difference* | *Essential hypertension* | *'Secondary' hypertension* | *Significance of between-diagnoses difference* | *Significance of between-sex difference for essential hypertension* |
| Average log plasma urea | 0·803 | 0·853 | P<0·05 | 0·744 | 0·755 | NS | P<0·001 |
| Number | 86 | 33 | | 90 | 44 | | |
| Annual increase in log urea | | | | | | | |
| (a) mean | 0·0065 | 0·0068 | NS | 0·0074 | 0·0068 | NS | NS |
| (b) Percentage with a positive increase | 72·1 | 75·8 | NS | 62·7 | 77·3 | NS | NS |
| Number | 86 | 33 | | 90 | 44 | | |

*Conversion SI to traditional units:* Plasma urea 1 mmol/l≈6.0 mg/100 ml.

was determined in 1294 patients referred to the Hammersmith Hospital hypertension clinic from 1952 to 1967 inclusive. A computer file was available, including age, sex, presenting blood pressure, and plasma urea. Seventy-seven patients were excluded as they were taking potent hypotensive drugs, leaving 614 men and 603 women. The computer record did not include details of diuretic therapy or diagnoses.

**Group 3** This group consisted of 283 patients attending for follow-up during 1973 who presented originally while not receiving any treatment and had a diagnosis of essential hypertension.

### Biochemical methods

All biochemical measurements were made in the Department of Chemical Pathology, at the Royal Postgraduate Medical School. The plasma urea was measured by the diacetyl monoxime method, using an autoanalyser after 1958.

### Statistical methods

The biochemical data were examined for statistical normality. Plasma urea (in mmol/l) had a log-normal distribution and was converted to a normal distribution by taking the logarithm of each observation. Many patients in group 1 had had more than one measurement in a year, and the averages (arithmetic means) of the transformed plasma ureas were calculated for each patient and each year together with the corresponding average dates. From these data the average log urea and age were computed for the period of follow-up and the annual increment in plasma urea was computed by a least squares regression of the yearly averages on time. Theoretical confidence limits for the observed data were computed by the standard method (Armitage, 1971).

In groups 2 and 3 independent effects on plasma urea of age and blood pressure were computed for the two sexes by standard multiple regression techniques. The mean blood pressure was calculated as the diastolic pressure plus a third of the pulse pressure.

## Results

Table 1 shows the average log urea during follow-up in group 1 and the average log urea increment according to sex and the type of hypertension. The average log urea was higher in men than women and in men with 'secondary' hypertension compared with those thought to have essential hypertension. Between 63 and 77 per cent of the patients had a positive increase in log urea during the follow-up period. The average annual increment in urea was 0·007 log mmol/l per year. It did not differ significantly between the groups but was significantly different from zero ($P < 0{\cdot}0001$). The 90 per cent confidence limits for a single estimate were −0·02 and +0·03 log mmol/l per year in both men and women. Five per cent of patients would, therefore, be expected to have an annual log increment greater than +0·03. The annual increase in untransformed plasma urea increased with the starting plasma urea concentration. Taking a logarithmic transformation of plasma urea resulted in an annual increment in log urea independent of the urea concentration achieved.

Table 2 lists the annual increments in plasma urea which would be expected to be exceeded by 5 per cent of a hypertensive population according to the initial plasma urea.

Table 3 shows the average results for group 2. Both plasma urea and diastolic pressure were higher in men. In this sample the plasma urea varied between 1·7 mmol/l and 79·2 mmol/l, age between 12 and 84 years, and mean blood pressure between 93 and 233 mmHg (12·4 and 31·0 kPa).

Tables 4 and 5 show the average log urea for both men and women in group 2 according to age and presenting mean blood pressure. In men the average log urea fell between the fourth and sixth decades rising again in the seventh decade. In women over 40 there was a rise with age, accelerating from the fifth to the seventh decade. In both sexes the plasma urea increased with the mean blood pressure.

The best correlation between blood pressure and log urea was with diastolic blood pressure in men and mean blood pressure in women. The correlation between mean blood pressure and log urea was also good in men, and mean blood pressure was used to predict log urea in both sexes. The following relation between urea, age, and mean blood pressure was found in men:

$$Y = 0{\cdot}8326 - 0{\cdot}016240A + 0{\cdot}000149A^2 + 0{\cdot}002676M \qquad (1)$$

Where Y is log plasma urea in log mmol/l, A is age in years, M is mean blood pressure in mmHg.
($n=614$, $R^2=0{\cdot}094$, square of age partial regression coefficient being significant at the 1% level, and age and mean blood pressure coefficients at the 0·1% level).

Similarly, in women:

$$Y = 0{\cdot}6830 - 0{\cdot}008873A + 0{\cdot}000113A^2 + 0{\cdot}001446M \qquad (2)$$

($n=603$, $R^2=0{\cdot}056$, the partial regression coefficient for age being significant at the 1% level and those for the square of age and mean blood pressure at the 0·5% and 0·1% level, respectively).

The prediction equations explained only 9 per cent of the variation in plasma urea in men and 6 per cent in women.

Comparing the sexes, Tables 4 and 5 show that a higher average log plasma urea in men is present in the younger age groups and is not noticeable above the age of 60. Similarly, the difference between the average log plasma urea in men and the average in women is more pronounced at a presenting mean blood pressure greater than 170 mmHg (22·6 kPa), than at lower presenting pressures.

The effect of blood pressure level on log urea concentration was more pronounced in men than in women, the partial regression coefficients (standardized for age) of log urea on mean blood pressure for the sexes being significantly different at the 5 per cent level. The increase in plasma urea with age was similar in the two sexes only after the sixth decade.

The relation between plasma urea and blood pressure was similar when the analysis was confined to patients presenting with essential hypertension and not receiving any treatment (group 3). On average a rise of 1 mmHg (0·1 kPa) mean pressure was associated with a 0·0020 log mmol/l rise in plasma urea in men and a 0·0011 log mmol/l rise in women.

TABLE 2 *Annual increment in plasma urea in mmol/l per year exceeded by theoretical 5 per cent of hypertensive patients and according to initial plasma urea*

| *Initial plasma urea (mmol/l)* | *Upper limit for annual increment (mmol/l per year)* |
|---|---|
| 2 | 0·14 |
| 4 | 0·28 |
| 8 | 0·57 |
| 16 | 1·14 |

*Conversion SI to traditional units:* Plasma urea, 1 mmol/l≈ 6 mg/100 ml.

## Discussion

### Increase in plasma urea with time or age

Equations (1) and (2) indicate that, pressure remaining constant, an increase in age of between 40 and 80 years would give an annual increase in log urea of 0·002 in hypertensive men and 0·005 in hypertensive women. (Increase in untransformed

TABLE 3 *Details of patients presenting to clinic between years 1952 and 1967, and not receiving potent hypotensive drugs (group 2)*

| | *Men* | *Women* | *Significance of difference* |
|---|---|---|---|
| Number | 614 | 603 | — |
| *Average* | | | |
| Plasma urea (mmol/l) | 8·23 | 6·68 | P<0·001 |
| Log plasma urea | 0·832 | 0·759 | P<0·001 |
| Systolic pressure (mmHg) | 211·56 | 211·44 | NS |
| Diastolic pressure (mmHg) | 127·20 | 122·19 | P<0·001 |
| Age (y) | 48·12 | 49·00 | NS |

*Conversion SI to traditional units:* Plasma urea, 1 mmol/l≈ 6 mg/100 ml.

TABLE 4 *Average log plasma urea in mmol/l for males in 28 groups subdivided according to presenting mean blood pressure and age*

| | *Mean blood pressure (mmHg)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Age (y)* | *≤130* | *–140* | *–150* | *–160* | *–170* | *–180* | *>180* | *All pressures* |
| 40 | 0·743 (36) | 0·774 (30) | 0·867 (20) | 0·832 (9) | 0·943 (25) | 1·159 (14) | 0·953 (20) | 0·868 (154) |
| –50 | 0·723 (20) | 0·832 (17) | 0·795 (23) | 0·774 (35) | 0·810 (29) | 0·853 (20) | 1·051 (19) | 0·825 (168) |
| –60 | 0·765 (24) | 0·765 (32) | 0·780 (35) | 0·872 (39) | 0·843 (32) | 0·847 (25) | 0·829 (28) | 0·816 (215) |
| >60 | 0·845 (6) | 0·787 (10) | 0·787 (15) | 0·769 (17) | 0·821 (14) | 0·900 (9) | 0·967 (6) | 0·821 (77) |
| All ages | 0·752 (86) | 0·783 (89) | 0·803 (98) | 0·817 (100) | 0·855 (100) | 0·921 (68) | 0·932 (73) | 0·832 (614) |

Figures in parentheses are numbers contributing to each average. Plasma urea increases with level of presenting blood pressure (group 2). *Conversion from traditional to SI units:* 1 mmHg≈0.133 kPa.

urea 0·03 mmol/l per year for an initial plasma urea of 6·3 mmol/l in men and an increase of 0·06 mmol/l per year for an initial urea of 5·5 mmol/l in women.) The hypertensive patients, when treated, had an average increase of +0·007 per annum (0·1 mmol/l per year for an initial urea of 6·0 mmol/l). The greater rise in plasma urea per annum during follow-up is possibly the result of treatment as it is recognized that diuretics and adrenergic neurone-blocking drugs increase plasma urea (Dinon, Kim, and Vander Veer, 1958; Bulpitt, 1974). However, we are comparing the results from cross-sectional and longitudinal studies. Early death from renal failure ensures that a patient is not included in a longitudinal study and the average increase of +0·007 must be an underestimate. Similarly the failure of a patient to survive to a certain age prevents his inclusion in a cross-sectional study, and patients with a high plasma urea will be poorly represented in the older decades. The average increments of +0·002 to 0·005 are presumably also underestimated.

Many cross-sectional studies have found normal subjects to have a rise in plasma urea with age. Taking a logarithmic transformation of the urea values reported in these studies, there have been reports of a greater rise in log plasma urea in women, 0·002 per annum, as opposed to 0·001 for men (Campbell *et al.*, 1968); similarly 0·002 per annum for women and no significant increase in men (Roberts, 1967), and rises in log urea of 0·002 (Keating *et al.*, 1969), and 0·001 per annum (Josephson and Dahlberg, 1952) for both men and women.

The use of different techniques in determining plasma urea makes it difficult to compare the absolute values of plasma urea in this study with those in 'normal' populations. However, the average plasma urea for men in this study with essential hypertension (6·3 mmol/l) was at the upper limit of the 'normal' range accepted by many laboratories, and the corresponding average for women with essential hypertension was 5·5 mmol/l. An average of 5·3 to 5·8 mmol/l and 4·0 to 5·3 mmol/l would be expected for men and women, respectively (Mackay and Mackay, 1927; Campbell *et al.*, 1968; Josephson and Dahlberg, 1952). The average plasma urea and annual increment in plasma urea are, therefore, increased in hypertensive patients, especially as the quoted increases in log urea per year of age in normal subjects were not adjusted for increases in blood pressure with age.

TABLE 5 *Average log plasma urea in mmol/l for females in 28 groups subdivided according to presenting mean blood pressure and age*

| | *Mean blood pressure (mmHg)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Age (y)* | *≤130* | *–140* | *–150* | *–160* | *–170* | *–180* | *>180* | *All pressures* |
| 40 | 0·685 (45) | 0·704 (31) | 0·674 (28) | 0·821 (24) | 0·783 (14) | 0·774 (14) | 0·758 (9) | 0·725 (165) |
| –50 | 0·705 (22) | 0·713 (21) | 0·707 (21) | 0·813 (17) | 0·673 (25) | 0·792 (17) | 0·874 (11) | 0·740 (135) |
| –60 | 0·732 (19) | 0·733 (33) | 0·753 (33) | 0·791 (27) | 0·759 (23) | 0·737 (22) | 0·800 (16) | 0·763 (178) |
| >60 | 0·804 (19) | 0·843 (15) | 0·751 (20) | 0·790 (20) | 0·837 (25) | 0·835 (14) | 0·903 (12) | 0·819 (125) |
| *All ages* | 0·719 (105) | 0·738 (100) | 0·723 (102) | 0·803 (88) | 0·762 (93) | 0·791 (67) | 0·836 (48) | 0·759 (603) |

Figures in parentheses are number contributing to each average. Plasma urea increases with both age and presenting mean blood pressure (group 2). *Conversion from traditional to SI units* · 1 mmHg≈0.133 kPa.

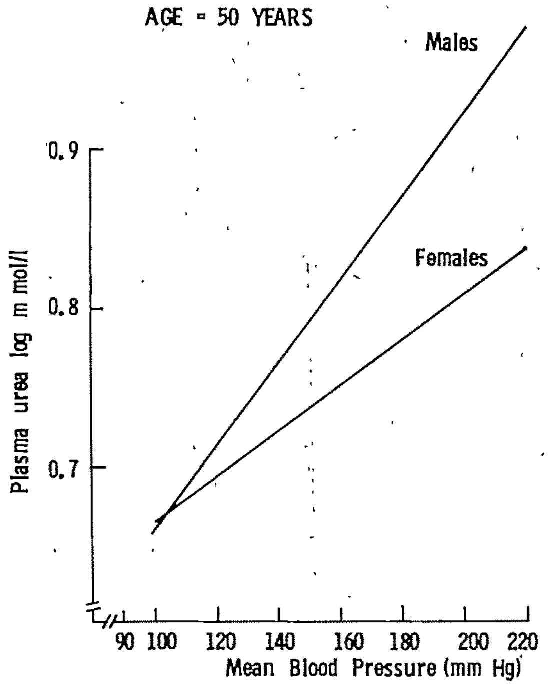

FIG. 1 *Relation between urea (log mmol/l) and presenting mean blood pressure for both sexes and after standardizing for age 50 years. All 1217 patients presented between the years 1952 and 1967.* Conversion: SI to traditional units—*Urea: 1 mmol/l ≈ 6·0 mg/100 ml.*

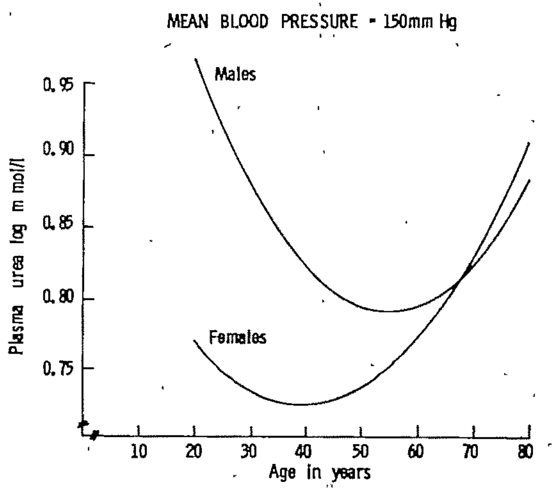

FIG. 2 *Relation between urea (log mmol/l) and age at presentation for both sexes and after standardizing for mean blood pressure of 150 mmHg (20·0 kPa). All 1217 patients presenting between the years 1952 and 1967.*

## Relation between plasma urea and presenting blood pressure

The blood pressure was important in determining the concentration of plasma urea on presentation to the clinic—the higher the untreated blood pressure the higher the plasma urea. The blood pressure in untreated patients may be raised as a consequence of renal dysfunction, whereas the blood pressure during treatment may well be more related to the hypotensive drugs given than to renal function. This might explain the presence of a correlation between plasma urea and blood pressure in untreated patients, whereas treated patients did not show a significant positive correlation (Bulpitt, 1974).

Interestingly, the presenting blood pressure was more closely related to the plasma urea in men than in women. The plasma urea increased, on average, by 0·04 mmol/l in men and 0·02 mmol/l in women for every 1 mm increment of presenting mean blood pressure.

The difference between the sexes in the relation both between age and plasma urea and mean pressure and urea may be related to the duration of hypertension. The two sexes have similar blood pressures at the ages of 5 to 8 (Beresford and Holland, 1973) but male subjects have an increase in pressure between the ages of 10 and 20, after which systolic, and to some extent diastolic, pressure remain fairly constant until the age of about 50 (Miall and Lovell, 1967). Women show a consistent rise in both diastolic and systolic pressure from childhood resulting in higher levels than men after the age of 40. These cross-sectional studies have been confirmed to some extent by longitudinal studies. Johnson, Karunas, and Epstein (1973) reported increases in systolic pressure for males aged 10 to 19 and 55 to 74 which were not so striking in females.

A longer exposure to a high pressure may explain the larger regression coefficient in men when log urea is regressed on pressure. This is supported by Fig. 1 where log urea is plotted against mean blood pressure according to equations (1) and (2) and for patients aged 50 years. The log urea is similar for the two sexes when the mean pressure is near normal and the patients cannot have been exposed to high pressures for any length of time.

In Fig. 2 log urea is plotted against age for a mean pressure of 150 mmHg (20·0 kPa). Over the age of 60 both men and women hypertensive patients may have been exposed equally to hypertension for many years and the log urea is similar for the two sexes. Below the age of 50 men may have been exposed to a high pressure for a relatively long interval and their plasma urea concentrations are greater.

The results for group 3 indicate that the relation between plasma urea and presenting blood pressure was not due to either diuretic therapy or the inclusion in group 2 of some patients with 'secondary' hypertension, the increases in plasma urea with mean pressure being similar for both groups 2 and 3. As group 2 was larger and less affected by non-survival, only the results for this group are presented in detail (equations (1) and (2)).

The relation between mean blood pressure and log urea may be a causal relation, a high pressure causing a deterioration in renal function. If the duration of raised pressure is important the between-sex differences in these relations may be explained, and possibly renal function may be preserved by the earlier detection and treatment of hypertension. The alternative hypothesis is that changes in renal function raise blood pressure. While receiving treatment any deterioration in renal function can be compared with the upper limits for annual increment shown in Table 2.

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# Circulatory response to vasodilator therapy in congestive cardiomyopathy[1]

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*Vasodilator therapy has been shown to have beneficial effects in heart failure. In order to evaluate the haemodynamic actions of vasodilator administration in primary congestive cardiomyopathy, sodium nitroprusside was infused intravenously at a rate of 15 to 100 μg/min to 12 patients. Mean arterial pressure fell 15 per cent from 86±3·0 to 72±2·4 mmHg (11·40±·4 to 9·6±0·3 kPa), and there was a small but significant decrease in mean heart rate from 96±4·8 to 90±4·4 beats/min. These changes were accompanied by a significant decrease in mean pulmonary artery pressure from 40±2·2 to 26±2·8 mmHg (5·3±0·3 kPa to 3·5±0·4 kPa), mean pulmonary capillary wedge pressure from 25±2·2 to 16±2·1 mmHg (3·3±0·3 to 2·1±0·3 kPa), and left ventricular end-diastolic pressure from 27±1·8 to 17±1·5 mmHg (3·6±0·3 to 2·3±0·2 kPa). Cardiac index increased by an average of 48 per cent from 2·1 to 3·1 l/min per m$^2$, and left ventricular stroke work index increased from 18·4±1·6 to 21·3±1·9 g m/m$^2$. These results show that pronounced left ventricular dysfunction in patients with congestive cardiomyopathy is improved during vasodilator therapy.*

The clinical course in congestive cardiomyopathy is frequently marked by repeated episodes of cardiac failure. Progressive left ventricular dilatation is accompanied by increased left ventricular wall stress, decreased myocardial efficiency, and further depression of myocardial performance. The prognosis of these patients is poor, with almost 50 per cent dying within 12 months of the onset of pulmonary congestion, and two-thirds dying within 2 years (Hamby *et al.*, 1970).

Prolonged periods of bed rest have been advocated with modest results (McDonald, Burch, and Walsh, 1971). Diuretics and inotropic agents have been the traditional methods of treatment in an attempt to decrease left ventricular filling pressure and increase cardiac output. Such therapy may initially produce symptomatic relief; however, further deterioration is inevitable, and a downhill course ensues. Reliance on the digitalis glycosides in the setting of cardiomyopathy is associated with a high incidence of toxicity.

Reflex arteriolar vasoconstriction in heart failure produces an increased systemic vascular resistance and impedance to left ventricular ejection, further depressing myocardial function. Recently, vasodilator therapy has been shown to improve left ventricular function in patients with congestive heart failure of diverse aetiologies (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a). In order to assess the potentially beneficial haemodynamic effects of a vasodilator agent in congestive cardiomyopathy, 12 patients were studied before and during nitroprusside infusion.

## Subjects and methods

Twelve patients with congestive cardiomyopathy were investigated at the time of diagnostic cardiac catheterization. Informed consent was obtained after the nature of the study and risks were explained in detail to the patients. The subjects comprised 11 men and one woman, ranging in age from 21 to 65 years, with a mean age of 43 years. Clinically, all patients had symptoms of New York Heart Association Class III or IV severity. All had ventricular ($S_3$) gallop sounds and cardiomegaly. There was no history of hypertension, valvular disease, or ischaemic heart disease. Normal coronary arteries and diffuse left ventricular hypokinesis were shown angiographically in all patients, using the

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transfemoral retrograde arterial approach. All patients were taking digitalis and diuretics at the time of the study.

At cardiac catheterization, right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge phasic and mean pressures were recorded with a 7F Cournand catheter inserted via an antecubital vein and connected to a Stratham P23Db transducer. Arterial and left ventricular pressures were determined by percutaneous transfemoral catheterization with a 6·7F end-hole catheter connected without tubing to a micron MP-15 transducer. The frequency response of the catheter-preamplifier system was flat to 14 Hz. Zero pressure reference level was taken at mid-chest.

Cardiac output was determined by the Fick technique, using the arteriovenous $O_2$ difference and a 5-minute collection of expired air. Pulmonary vascular resistance and systemic vascular resistance were computed, using standard formulae. Left ventricular stroke work index was calculated using the mean left ventricular systolic pressure.

After control measurements, nitroprusside was infused intravenously, initially at a rate of 15μg/min. The infusion rate was increased every 2 minutes by 15μg/min until the mean arterial pressure had dropped by a minimum of 10 mmHg (1·3 kPa). Nitroprusside infusion rates of 15 to 100μg/min were needed. Haemodynamic measurements were repeated after 10 minutes of continuous nitroprusside infusion, maintaining the desired arterial pressure. Statistical analysis was carried out using Student's t-test for paired data.

## Results

The Table summarizes the haemodynamic data in the 12 patients receiving nitroprusside. All were in sinus rhythm except one who was in atrial fibrillation. Nitroprusside produced an average fall in mean arterial pressure of 16 per cent from 86±3·0 to 72±2·4 mmHg (11·4±0·4 to 9·6±0·3 kPa). There was a small but statistically significant fall in heart rate from an average of 96±4·8 to 90±4·4 beats/min. Two patients had a modest increase in heart rate; there was no haemodynamic measure that separated them from the rest of the group. Right atrial mean pressure fell 36 per cent. Mean pulmonary artery pressure fell from 40±2 to 26±2·8 mmHg (5·3±0·3 to 3·5±0·4 kPa) (range 6 to 28 mmHg (0·8 to 3·7 kPa)), mean pulmonary capillary wedge pressure fell from 25±2·2 to 16±2·1 mmHg (3·3±0·3 to 2·1± 0·3 kPa) (range 3 to 26 mmHg (0·4 to 3·5 kPa)), and left ventricular end-diastolic pressure fell from 27±1·8 to 17±1·5 mmHg (3·6±0·3 to 2·3±0·2 kPa) (range 6 to 22 mmHg (0·8 to 2·9 kPa)). These changes were all statistically significant and of similar magnitude (P<0·001,

TABLE *Clinical and haemodynamic data in 12 patients receiving nitroprusside*

| *Case No., sex* | *R* | *HR (beats/min)* | | *$\overline{RA}$ (mmHg)* | | *$\overline{PA}$ (mmHg)* | | *$\overline{PCW}$ (mmHg)* | | *MAP (mmHg)* | | *LVEDP (mmHg)* | | *CI (l/min per m²)* | | *LVSWI (g m/m²)* | | *PVR (RU)* | | *SVR (RU)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* | *C* | *NP* |
| 1/M | NSR | 88 | 68 | 5 | 5 | 42 | 27 | 33 | 23 | 79 | 68 | 32 | 26 | 2·6 | 3·2 | 22·4 | 29·2 | 2·0 | 0 7 | 16·1 | 10·8 |
| 2/M | NSR | 71 | 84 | 23 | 14 | 53 | 46 | 36 | 33 | 93 | 80 | 32 | 23 | 2 1 | 3·9 | 16·3 | 18 4 | 6·3 | 3·4 | 34 1 | 17·1 |
| 3/M | NSR | 120 | 110 | 23 | 15 | 47 | 37 | 28 | 18 | 104 | 75 | 26 | 16 | 2·4 | 3·7 | 26·5 | 28·8 | 3 9 | 0·8 | 16·8 | 7 9 |
| 4/M | NSR | 90 | 82 | 4 | 0 | 49 | 21 | 37 | 11 | 76 | 68 | 42 | 20 | 1·6 | 2 2 | 11·2 | 15·4 | 4 5 | 2 8 | 28 0 | 19·1 |
| 5/M | NSR | 108 | 96 | 9 | 6 | 38 | 17 | 26 | 12 | 104 | 85 | 28 | 19 | 2·7 | 4·7 | 28·4 | 30·8 | 2·3 | 0 7 | 15 4 | 10·0 |
| 6/M | NSR | 80 | 75 | 8 | 4 | 28 | 18 | 16 | 13 | 76 | 66 | 20 | 14 | 2·1 | 2·7 | 19·8 | 20·3 | 2·9 | 1 0 | 16·5 | 12·2 |
| 7/M | NSR | 95 | 95 | 9 | 6 | 28 | 20 | 16 | 12 | 88 | 74 | 20 | 12 | 1 5 | 2 0 | 16 8 | 17·4 | 4·8 | 2 2 | 27 2 | 18·4 |
| 8/F | NSR | 84 | 87 | 11 | 7 | 42 | 22 | 26 | 14 | 86 | 80 | 26 | 12 | 2·1 | 4 6 | 20 4 | 30 6 | 4 2 | 1·0 | 20·3 | 8·9 |
| 9/M | AF | 108 | 96 | 10 | 8 | 40 | 28 | 18 | 16 | 70 | 60 | 23 | 16 | 2·0 | 2 6 | 16·2 | 17 8 | 2 8 | 1 1 | 19 6 | 9·9 |
| 10/M | NSR | 125 | 122 | 11 | 10 | 36 | 30 | 27 | 22 | 86 | 77 | 26 | 20 | 2·2 | 2 5 | 16·6 | 17 1 | 2 6 | 2·1 | 21·5 | 17·6 |
| 11/M | NSR | 83 | 75 | ·4 | 1 | 36 | 12 | 24 | 6 | 86 | 60 | 22 | 7 | 2 0 | 2 1 | 13·2 | 13 6 | 3 4 | 1·6 | 25·0 | 16·2 |
| 12/M | NSR | 98 | 92 | 11 | 5 | 39 | 32 | 20 | 10 | 88 | 80 | 23 | 14 | 1 8 | 2·6 | 12·6 | 16·1 | 6 5 | 5·0 | 26·5 | 18·3 |
| Mean | | 96 | 90 | 11 | 7 | 40 | 26 | 25 | 16 | 86 | 72 | 27 | 17 | 2·1 | 3 1 | 18 4 | 21 3 | 3·9 | 1·9 | 22·3 | 13·9 |
| ±SEM | | 4·8 | 4·4 | 1·8 | 1·3 | 2·2 | 2·8 | 2·2 | 2 1 | 3 0 | 2·4 | 1 8 | 1·5 | 0 2 | 0·3 | 1 6 | 1·9 | 0·4 | 0 4 | 1·7 | 1·2 |
| Mean%Δ | | −6% | | −36% | | −35% | | −38% | | −16% | | 37% | | +48% | | +16% | | −51% | | −38% | |
| P< | | 0·05 | | 0 001 | | 0·001 | | 0 001 | | 0 001 | | 0·001 | | 0·001 | | 0 01 | | 0·001 | | 0·001 | |

R=rhythm; HR=heart rate; $\overline{RA}$=right atrial mean pressure; $\overline{PA}$=pulmonary arterial mean pressure; $\overline{PCW}$=pulmonary capillary wedge mean pressure; MAP=mean arterial pressure; LVEDP=left ventricular end-diastolic pressure; CI=cardiac index; LVSWI=left ventricular stroke work index; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance; RU=resistance units; C=control; NP=nitroprusside; M=male; F=female; NSR=normal sinus rhythm; AF=atrial fibrillation; SEM=standard error of the mean; mean %Δ=mean percent change.

Fig. 1). The degree of these changes did not correlate directly with the magnitude of mean arterial pressure or systemic vascular resistance decrease during nitroprusside infusion.

There was a 48 per cent mean increase in cardiac index from 2·1±0·2 to 3·1±0·3 l/min per $m^2$ (range 0·3 to 2·5 l/min per $m^2$). The most pronounced increases occurred in those patients with the highest left ventricular end-diastolic pressure and greatest decrease in systemic vascular resistance (Fig. 2). Systemic vascular resistance fell an average of 38 per cent, and pulmonary vascular resistance was decreased in all patients by an average of 51 per cent.

Left ventricular stroke work index rose modestly but significantly from 18·4±1·6 to 21·3±1·9 g m/$m^2$ ($P<0{\cdot}01$). The increase in left ventricular stroke work index associated with a decrease in left ventricular end-diastolic pressure suggests improved ventricular function. The most pronounced increases in stroke work index occurred in 4 to 6 patients whose initial left ventricular end-diastolic pressure was greater than 25 mmHg (3·3 kPa). Fig. 3 shows this relation by means of a standard ventricular function curve analysis.

## Discussion

Patients with advanced cardiomyopathy suffer from refractory left ventricular failure. Standard therapeutic manoeuvres are aimed at increasing myocardial contractility by means of inotropic agents, and reducing left ventricular filling pressure by sodium restriction and diuretics. As the severity of pump dysfunction progresses, however, the response to such measures decreases, and intractable left ventricular failure results. In addition, intravascular volume reduction may further lower cardiac output and produce electrolyte abnormalities which may predispose to serious ventricular arrhythmias in such patients.

Recently, the importance of systemic vascular resistance and impedance to ejection have been emphasized as major determinants of left ventricular function (Cohn, 1973; Ross and Braunwald, 1964). As myocardial function decreases, the failing heart dilates, increasing end-diastolic fibre length to maintain stroke volume near normal levels (Braunwald, Ross, and Sonnenblick, 1967). Increases in ventricular filling pressure accompany the augmented

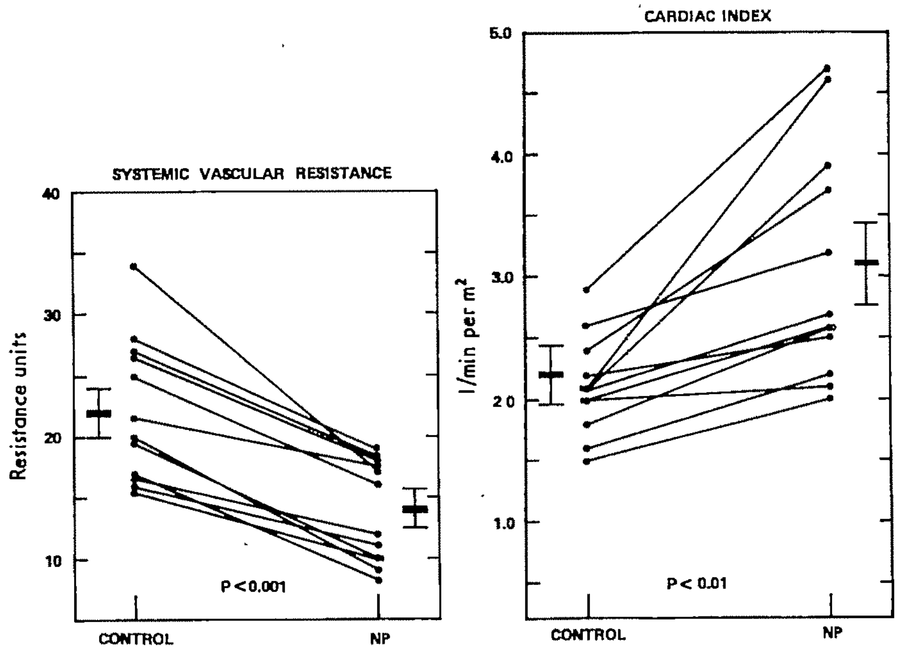

FIG. 1 Left—*change in systemic vascular resistance after nitroprusside infusion.* Right, *change in cardiac index after nitroprusside infusion. Heavy horizontal bars indicate mean values; lighter bars indicate standard error of mean. NP=nitroprusside.*

end-diastolic volume, producing symptoms of congestion. As cardiac output falls, reflex increases in circulating catecholamines produce arteriolar vasoconstriction to maintain mean arterial pressure (Chidsey, Harrison, and Braunwald, 1962; Kramer, Mason, and Braunwald, 1968). The rise in systemic vascular resistance produces an increased impedance to left ventricular ejection and, as a result, systolic ventricular wall tension or afterload is increased (Cohn, 1973). Increased afterload reduces the extent of myocardial fibre shortening, decreases the ejection fraction, and further limits pump performance (Ross and Braunwald, 1964).

Vasodilator therapy has recently been applied to patients with heart failure of various aetiologies, including acute myocardial infarction, cardiomyopathy, and mitral regurgitation (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a; Majid, Sharma, and Taylor, 1971; Walinsky *et al.*, 1974; Goodman *et al.*, 1974; Chatterjee *et al.*, 1973b). Nitroprusside was used in the present study to produce ventricular unloading in a group of patients with severe left ventricular failure. Nitroprusside infusion in our patients with chronic congestive cardiomyopathy produced haemodynamic improvement consistent with previous studies (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a; Miller *et al.*, 1975; Schlant, Tsagaris, and Robertson, 1962; Cohn *et al.*, 1972). Cardiac index and left ventricular stroke work index were significantly augmented while left ventricular filling pressure and right-sided cardiac pressures declined. The increase in forward output tended to parallel the fall in systemic vascular resistance (Table, Fig. 2). Thus, the reduction in impedance to left ventricular ejection produced by systolic unloading resulted in increased myocardial fibre shortening and increased stroke volume. Because heart rate, on the average, fell slightly, the increase in cardiac output primarily reflected increases in left ventricular stroke volume. In a group of patients with cardiomypathy and intractable heart failure, Guiha *et al.* (1974) showed haemodynamic improvement of a similar magnitude. It is of note that the majority of our patients had a high left ventricular end-diastolic pressure, which was significantly reduced by nitroprusside, but which remained abnormal above 12 mmHg (1·6 kPa). Miller *et al.*

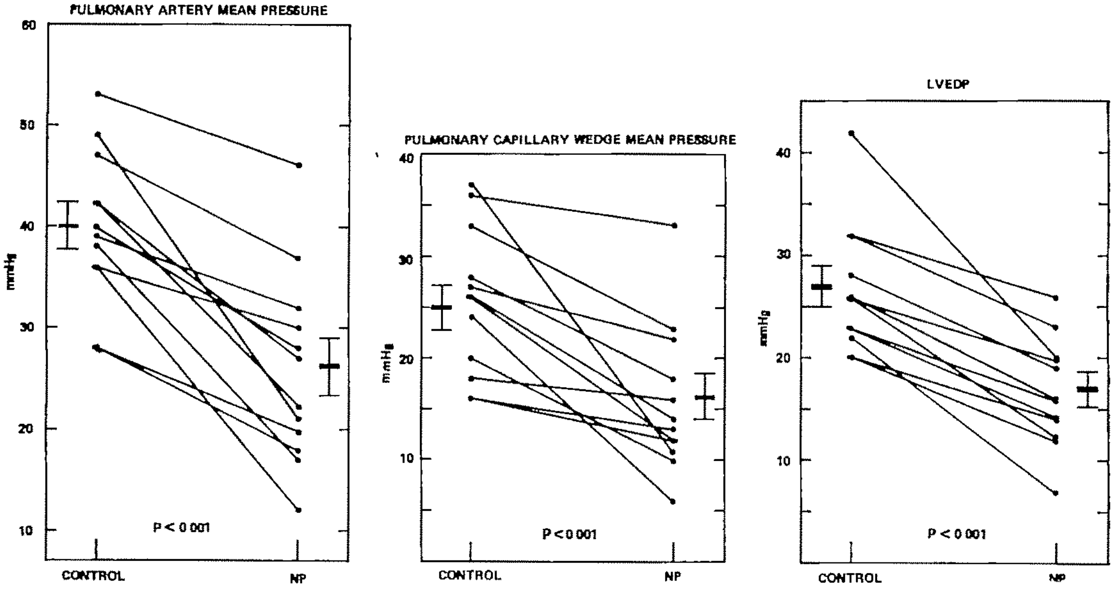

FIG. 2 Left—*change in pulmonary arterial mean pressure after nitroprusside infusion.* Centre—*change in pulmonary capillary wedge mean pressure after nitroprusside infusion.* Right—*change in left ventricular end-diastolic pressure (LVEDP) after nitroprusside infusion. NP—nitroprusside. Heavy horizontal bars indicate mean values; lighter bars indicate standard error of mean.*

(1975) noted that the usual beneficial response of cardiac index and heart rate to nitroprusside was not seen if left ventricular end-diastolic pressure fell below 10 mmHg (1·3 kPa). Fig. 3 supports this conclusion, in that those patients whose left ventricular end-diastolic pressure decreased to normal showed little improvement in pump performance, while those who retained some rise in left ventricular end-diastolic pressure had the greatest increase in stroke work index.

The mechanism of haemodynamic improvement during nitroprusside infusion is complex. It is clearly an arteriolar vasodilator, thus reducing systemic vascular resistance and ventricular afterload, enhancing myocardial fibre shortening, and increasing ejection fraction. In addition, nitroprusside decreases preload by dilating the peripheral venous bed (Miller *et al.*, 1975; Cohn *et al.*, 1974). Venodilatation may contribute to the lowering of systemic venous and left ventricular filling pressure. In our patients, reduction in outflow impedance appears to be primarily responsible for their improved ventricular performance.

Decreases in left ventricular end-diastolic and end-systolic volumes during nitroprusside infusion have been documented by echocardiography and angiography (Guiha *et al.*, 1974; Goodman *et al.*, 1974; Chatterjee *et al.*, 1973b; Miller *et al.*, 1975; Franciosa *et al.*, 1974). The reduction in chamber size decreases left ventricular wall tension. This, coupled with no increase in heart rate or contractile state, reduces myocardial oxygen requirements. Thus, stroke volume is increased and filling pressures are decreased in association with improved myocardial efficiency. Reduction in left ventricular volumes would be expected to decrease or abolish mitral regurgitation due to papillary muscle dysfunction, which is frequently encountered in these patients. Significant decreases in regurgitant volume and regurgitant fraction have been noted during vasodilator therapy in patients with mitral regurgitation of both valvular and subvalvular origin (Goodman *et al.*, 1974; Chatterjee *et al.*, 1973b).

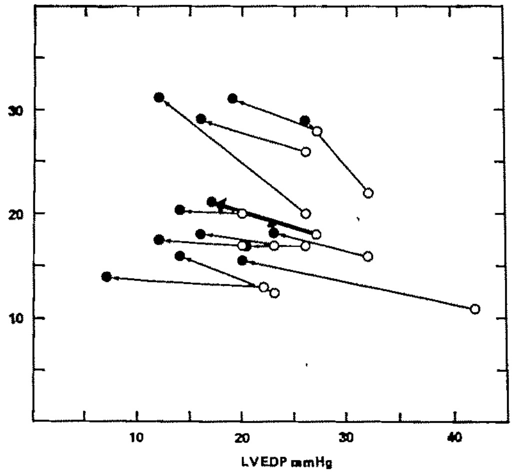

FIG. 3 *Effect of nitroprusside on left ventricular stroke work index and end-diastolic pressure. Individual patients are indicated by a line connecting an open circle (control) to a closed circle (nitroprusside). Arrows indicate direction of change. Heavy line indicates mean value. LVSWI=left ventricular stroke work index. LVEDP=left ventricular end-diastolic pressure.*

The improvement in pump performance with afterload reduction documented by the present study has potentially important clinical implications. The development of long-acting oral vasodilators may offer an alternative to chronic digitalis and diuretic therapy, with their attendant complications. Recently, haemodynamic improvement with oral isosorbide dinitrate has been described in patients with congestive heart failure (Franciosa *et al.*, 1974; Cohn *et al.*, 1974). It remains to be determined whether chronic afterload reduction by oral therapy will maintain left ventricular performance, prevent progressive ventricular dilatation, and improve the prognosis of patients with congestive cardiomyopathy.

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# Acute massive mitral regurgitation from prosthetic valve dysfunction

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*Two cases of prosthetic valve dysfunction resulting in acute massive mitral regurgitation are reported; emergency operation was successful in both cases. Survival following complete dislodgement of the occluder of a disc valve, as occurred in one case, does not appear to have been reported before. The difficulty in diagnosis of sudden cardiac decompensation in patients with prosthetic valves is stressed, as is the need for urgent operation.*

Prosthetic valve replacement is still associated with late complications with sufficient frequency to make it the operation of necessity rather than of choice. Thromboembolism and infection are the most commonly encountered problems and mechanical defects are reassuringly uncommon.

Acute massive mitral regurgitation from prosthetic valve dysfunction is particularly rare and usually rapidly fatal (Low and Lefemine, 1967; Samaan, 1969; Roberts and Morrow, 1968; Vasko and Leighton, 1968; Kalke *et al.*, 1969; Ibarra-Perez *et al.*, 1970; Wilson, 1970; DuPriest *et al.*, 1973; Messmer, Rothlin, and Senning, 1973; Keen, 1974). This paper reports two such cases, in each of which an emergency operation had a successful outcome.

## Case reports

### Case 1

The patient, a 47-year-old woman, had undergone mitral valve replacement in 1964 at another London hospital. A Type 1 University of Cape Town mitral valve prosthesis had been inserted.

In 1968 she developed a persisting fever and was found to have splenomegaly, anaemia, finger clubbing, and haematuria. Investigations showed raised titres for Q fever antibodies, strongly suggesting active endocarditis. She was treated with tetracycline and made a good symptomatic recovery.

In September 1969 she noticed acute, but transient (10 minutes) loss of vision of the left eye, followed by severe dyspnoea and palpitation. She was admitted to another hospital, by which time she was shocked and cyanosed with a sinus tachycardia of 140/minute, a blood pressure of 60/30 mmHg (8/4 kPa), and gross rise in the venous pressure. Tachycardia made auscultation difficult, but a soft systolic murmur could be heard over the whole praecordium. There were bilateral crepitations, and a chest *x*-ray film confirmed gross pulmonary oedema. An electrocardiogram showed sinus tachycardia but no other significant abnormality. She was treated with frusemide, digoxin, and morphine with no improvement. Endotracheal intubation and intermittent positive pressure ventilation were employed and the patient was transferred to The Middlesex Hospital.

On admission the clinical picture was of tachycardia and acute severe left and right ventricular failure. In view of her previous history and in the absence of evidence of another cause, prosthetic valve dysfunction was suspected and emergency exploration of the valve was carried out. At operation all heart chambers were found to be of normal size; left atrial and pulmonary arterial pressures were raised and the left atrium showed systolic expansile pulsation. The University of Cape Town prosthesis had fractured circumferentially between the rigid Ivalon seating of the valve and the spongy Ivalon sewing ring (Fig. 1). About a quarter of the circumference was still attached, corresponding to the medial half of the mural cusp of the mitral valve; the prosthesis was otherwise lying free in the atrium. The suture-bearing cuff of the valve appeared to be

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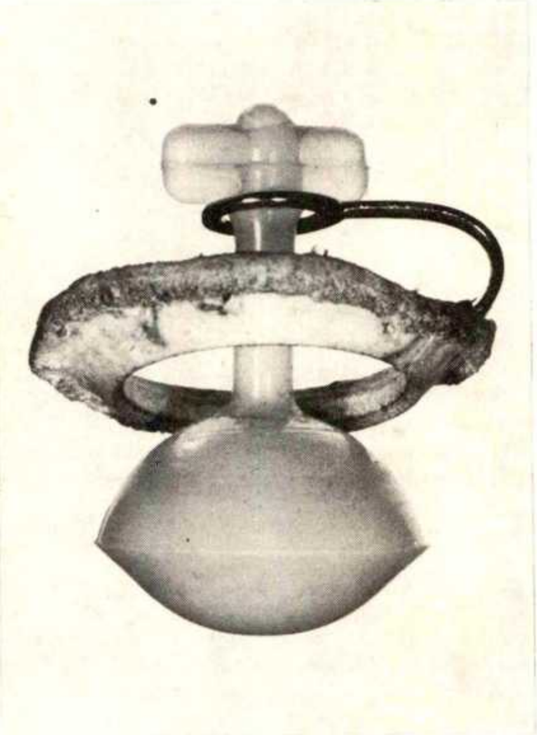

FIG. 1 *Excised University of Cape Town Type 1 mitral prosthesis (Case 1). The Ivalon ring had fractured circumferentially throughout three-quarters of its circumference. The peripheral flange was left in the patient.*

perfectly incorporated in the mitral annulus. There was no evidence of infection on the valve, which was perfectly clean, or in the left atrium, which contained no clot. At operation, separation of the prosthesis was completed, leaving the firmly-embedded sewing ring, and a No. 3M Model 6120 Starr-Edwards ball valve prosthesis was inserted.

The postoperative period was eventful, the patient developing tamponade, which was successfully relieved, and later, respiratory distress leading to cardiac arrest, which was successfully reversed after 30 minutes of cardiac massage. The patient remained ventilator-dependent until the sixteenth postoperative day, during which period a tracheostomy was performed; subsequent progress was satisfactory.

The response to animal inoculation with tissue obtained from the excised prosthesis showed the presence of *Rickettsia burneti,* but the antibody response obtained indicated non-viable organisms. A subsequent (November 1969) fall in antibody level in the patient's serum suggested an absence or suppression of *R. burneti* as an antigenic stimulus, but it was decided to continue suppression of this organism indefinitely, currently using demeclocycline.

She has since been followed up as an out-patient and was last seen in April 1975. She is able to lead a very active life and is employed full-time: she takes no medication except warfarin and demeclocycline. Her new mitral prosthesis continues to function well and the chest *x*-ray film shows only minimal cardiomegaly.

### Case 2

The patient was a 32-year-old male Yugoslav student studying in England. In 1969 he had undergone mitral valve replacement in the U.S.A., a No. 30 Wada-Cutter prosthesis being inserted. The patient progressed satisfactorily and remained symptomatically well without cardiac or anticoagulant drugs, though when he was first seen in this country in October 1973 a systolic murmur was heard. By December 1973, the murmur had increased and the patient was referred for a surgical opinion. Before any further investigation could take place, however, he developed acute dyspnoea accompanied by sudden chest pain, palpitation, and the production of profuse amounts of pink, frothy sputum, and was admitted as an emergency to The Middlesex Hospital.

The patient was cyanosed, cold, sweaty, and grossly dyspnoeic. The pulse rate was 150/minute, jugular venous pressure was not raised, and the blood pressure was 80/0 mmHg (10·7/0 kPa). The gross tachycardia made auscultation difficult, but it was thought that there was a third heart sound and a systolic murmur; there were no thrills. Coarse crepitations could be heard throughout the lungs.

Initial treatment with intravenous frusemide, digoxin, diamorphine, and hydrocortisone was given, but with little beneficial effect. An electrocardiogram showed atrial tachycardia, and chest *x*-ray examination showed gross pulmonary oedema; the prosthetic valve ring could be seen. DC countershock was unsuccessful in restoring normal rhythm, as were carotid sinus and eyeball pressure. The clinical picture of gross pulmonary oedema of sudden onset suggested serious dysfunction of the prosthesis and no other explanation of his abrupt deterioration seemed likely. It was agreed that immediate surgical exploration was needed. Positive pressure ventilation was initiated, and the trachea and main bronchi were sucked out at frequent intervals with good effect before the patient was transferred to the theatre.

At operation, gross mitral regurgitation was obvious from the systolic pulsation of the left atrium, though both left atrium and left ventricle were of normal size. When the left atrium was opened, the disc was found to be absent from the prosthesis. The left ventricle was explored, and the entire thoracic aorta was palpated via the left pleura, but the disc could not be found. The ring of the Wada prosthesis was excised, and a No. 3M Model 6120 Starr-Edwards prosthesis was inserted. The mid-line incision was extended and a hand was passed into the abdomen, but the disc was not palpable in the abdominal aorta or iliac arteries.

Postoperatively progress was initially slow, but basically uneventful. The new prosthesis functioned efficiently, and the pulmonary oedema cleared over the next few days. On the third postoperative day thoracic and abdominal aortography was carried out and a possible filling defect was seen at the aortic bifurcation; echocardiography also suggested that the disc might be present at this site. Laparotomy was performed on the 4th day and the disc was eventually found, not at the aortic bifurcation, but at the level of the renal vessels, behind the pancreas. It was removed through an incision in the lower descending aorta with some difficulty as it proved to be considerably larger than expected and had sharp protuberances.

The Teflon disc showed signs of wear at the pivot sites where it had been bearing on the metal retaining struts of the prosthesis (Fig. 2). Notching had occurred at these points, allowing the disc to open more than its design intended until eventually it had slipped out of position entirely.

Twenty-seven days after his admission the patient was well enough to be discharged home, and at this time was taking digoxin, frusemide, slow K, and warfarin. Later, all medication was stopped, with the exception of the anticoagulant. The patient has since been seen on three occasions as an out-patient, most recently in July 1974. His progress has been excellent; there are no cardiac murmurs, and chest *x*-ray examination shows further improvement. He had returned to full-time employment and has since emigrated to Australia.

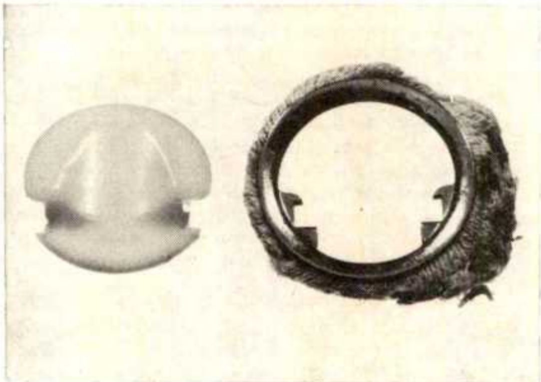

FIG. 2 *Excised ring and dislocated disc of Wada-Cutter mitral prosthesis (Case 2), showing notching of disc at points of contact with retaining struts of the ring.*

## Discussion

Both cases illustrate a design problem of prosthetic valves where mobile elements join or impinge on rigid elements of the structure. However, in reporting seven years' experience with four models of the University of Cape Town prosthesis in 122 patients, Schrire and Barnard (1970) did not meet the complication described in the present paper.

The greatest experience with the Wada-Cutter valve has been reported from Houston, Texas, where 150 patients had valves replaced by this prosthesis during 1969 (Hallman *et al.*, 1970). No cases of dysfunction of the prosthesis in the mitral position were reported after a follow-up period of approximately one year. In 1972, Wada reported that he had used this valve in 106 patients, including 48 in the mitral position, and in only one case was replacement of a defective prosthesis necessary (Wada, Komatsu, and Kamata, 1972).

Complete dislodgement of a Wada-Cutter disc valve occluder has been reported previously on one occasion. In 1973, DuPriest and his colleagues reported the sudden death of a 48-year-old man whose mitral valve had been replaced three years earlier. Gross pulmonary oedema and congestion were noted at necropsy, and the disc was found at the apex of the left ventricle. The disc had a notch at one pivot point and was thinned at the other pivot point. At an angle of 50°, the disc slipped from the four projections which ordinarily retain it. As in our own case the disc had become dislodged because of wearing of the Teflon; DuPriest and his colleagues forecast that further cases would occur, and suggested that as durable alternatives were available continued clinical use of the Wada-Cutter valve should be reconsidered.

Björk (1970) also reported variance of Wada-Cutter valves (in the aortic position) with grooving of the Teflon disc where it strikes the metal shoulder of the valve ring; this had led to the death of two patients within one year, though in neither case was this the result of dislodgement of the disc. Pulse duplicator studies showed that the Teflon disc of the Wada prosthesis was more susceptible to wear than discs of other materials used in the construction of prostheses.

Disc dislodgement has occurred from a Björk-Shiley mitral prosthesis (Messmer *et al.,* 1973), and a case of dislodgement of a deformed silicone rubber ball from a Cutter-Smeloff prosthesis has been reported by Keen (1974). The case of disc dislodgement reported in the present paper had a successful outcome, and in this respect appears to be unique. If the poppet had been a ball rather than a disc, it is probable that total occlusion of the aorta would have occurred leading to a sudden increase in peripheral resistance, left ventricular embarrassment, and sudden death as in Keen's case. The present case also emphasizes the difficulty in locating a disc embolus; all peripheral pulses were present, and neither radiography nor echocardiography located it accurately.

Several authors have stressed the difficulty in making a definite diagnosis in prosthetic valve dysfunction, particularly in the early postoperative period. Auscultation, phonocardiography, echocardiography, and fluoroscopy may be inconclusive; left heart catheterization with cineangiography appears to be the only reliable means of confirming the diagnosis (Thomas, 1971), but may be precluded by the urgency of the situation. Absence of the opening click is an ominous sign of malfunction of ball or disc valve prostheses, whether this sign is the result of insufficient perpendicular force to move the occluder from thrombus or tissue ingrowth, swelling of the poppet itself, or complete absence of the ball or disc. Leachman and Cokkinos (1969) have reported 6 cases of dehiscence of a disc valve in which the characteristic opening click of the prosthesis was absent, and concluded that if the absence of the click can definitely be documented, such a patient should be considered for corrective surgical therapy at the earliest possible time. Auscultation, however, may be exceedingly difficult in such cases, because of extreme tachycardia, the obviously small cardiac output, and the loud pulmonary added sounds. With free reflux, a systolic murmur is not present, but a third sound may be heard. Phonocardiography has been used in conditions of malfunction of mitral valve prostheses and may prove helpful in confirming auscultatory signs (Craige, Hutchin, and Sutton, 1970; Wise, Webb-Peploe, and Oakley, 1971).

The two cases reported here illustrate the difficulty in diagnosis. It is our view, however, that a patient with a prosthetic valve, who experiences sudden cardiac decompensation that cannot be readily attributed to a pathological cause such as myocardial infarction, or speedily controlled medically, should be re-explored urgently for prosthetic dysfunction. Operation should not be delayed to permit sophisticated investigation which may confirm the diagnosis but vitiate treatment.

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# Retrograde conduction in complete atrioventricular block
## *Study using His bundle recordings*

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*Using His bundle recordings and ventricular stimulation retrograde conduction was studied in 57 cases of complete AV block. VA conduction was observed in 13 patients. Of the 13, 12 had AV block distal to H, and during cardiac pacing 5 of them showed a retrograde His bundle potential. In all cases the AV node-His pathway was implicated in the transmission of the retrograde impulse. There was no retrograde atrial response in the remaining patients. VA block usually occurred at the same level as AV block. Nevertheless, two cases of AV block distal to H were associated with concealed retrograde conduction which stopped within the AV node.*

Inverted atrial depolarizations in advanced or complete atrioventricular (AV) block could be regarded as paradoxical. They suggest a persisting ventriculoatrial (VA) conduction while forward transmission is interrupted. Such phenomena have always been considered rare. Ten years ago Scherf and Cohen (1964), reviewing the published reports, found 81 cases, including the first clinical report by Cohn and Fraser (1913).

The use of cardiac stimulation in the treatment of AV block has enabled the 'reversed conduction' phenomenon to be observed more often. Thus, Adams (1963) noted the occurrence of retrograde P waves after the insertion of a ventricular pacemaker in a patient with complete AV block. Other cases have been reported since (Hafemeister and von Knorre, 1968; Santoli *et al.*, 1969; Puech *et al.*, 1970b). The recent development of clinical electrophysiological studies has also brought added interest in this field (Castillo and Samet, 1967; Goldreyer and Bigger, 1970).

In the present investigation retrograde conduction in complete heart block was studied during ventricular pacing. Recordings of His bundle activity were made to localize the site of AV and VA block and to identify the pathways of retrograde conduction.

## Subjects and methods

All of the 57 patients included in the study had been admitted between January 1972 and March 1973 to the intensive care unit for syncope resulting from complete AV block. Informed consent was obtained from each patient. There were 21 men and 36 women ranging in age from 36 to 85 years (average 71). The external electrocardiogram showed atrial activity originating in the sinus node and a ventricular escape rhythm, the rate of which ranged from 30 to 65 per minute. The QRS complexes were narrow in 10 cases and wide in 47.

The electrophysiological study included the recording of the His bundle potential (H) by Scherlag's method (Scherlag *et al.*, 1969). The proximal terminals of the electrode-catheter were connected to the input of an electrocardiograph amplifier (recording frequencies 50 to 700 Hz). A bipolar atrial electrogram was simultaneously recorded via an electrode-catheter positioned at the upper part of the right atrium. Complete absence of AV conduction was checked by atrial pacing at increasing rate. Right ventricular pacing was initiated at a rate slightly faster than the spontaneous heart rate, and increased by increments of 10 to 20 beats/min up to 160/min. The impulses, 2 ms in duration, were delivered by a Medtronic 5837 stimulator at twice diastolic threshold intensity.

The studies were carried out in the postabsorptive non-sedated state. Each patient was under continuous monitoring. Lead II was visualized on an oscilloscope. An Elema four-channel recorder was used. The paper speed was 50 to 100 mm/s. At the end of the study the ventricular catheter was usually left in place until the insertion of a permanent pacemaker.

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## Definition of terms

The site of the AV block was defined as follows (Puech *et al.*, 1970a; Narula *et al.*, 1971).

1) Block proximal to H, involving the AV node or the initial part of the main bundle. The electrogram of the His bundle was dissociated from the atrial activity but preceded each ventricular escape complex.
2) Block at the H recording site—that is, in the main bundle itself. The His potential was divided into two independent components, one of which followed atrial activity and the other initiated ventricular rhythm.
3) Block distal to H, located either at the extremity of the main bundle or in both branches. The His bundle electrogram followed each atrial wave and was independent of the ventricular impulses.

A and V represented, respectively, the atrial and ventricular activities recorded in the His bundle lead.

Similarly, the level of the retrograde block was defined in relation to the H deflection. The VA block was assumed to be infra- or intra-Hisian if an unchanged AH conduction persisted during ventricular pacing. On the other hand, a supra-Hisian VA block was defined by the absence of H deflection following the atrial activity, the retrograde His bundle depolarization H′ being included in, or observed after the ventricular activity.

In VA conduction the atrial activation sequence was reversed: the A wave in the His bundle lead then preceded the high atrial electrogram.

## Results

Of the 57 cases with complete AV block 3 were proximal to H, 11 involved the main bundle, and 43 were distal to the recording site of the His bundle activity. VA conduction was present in 13 patients (22%) (Table); 12 of them had an AV block distal to H (Fig. 1, 3, and 4) and only one proximal to H (Fig. 2). No retrograde conduction to the atria was observed in the remaining group. The VA block was located at the same level as the AV block. However, two cases of infra-Hisian block showed an intermittent retrograde conduction to the His bundle and to the AV node (Fig. 5).

## Discussion

The inverted atrial responses sometimes seen in high-grade AV block are usually explained by the persistence of retrograde conduction to the atria, despite complete, or nearly complete, interruption of the AV conduction. Other theories based on the influence of the ventricular contraction on the atrial activity or the passive propagation of electrotonic currents (Scherf, 1959) are more questionable. To explain the 'reversed conduction' phenomenon, Danielopulu and Danulesco (1922) postulated the existence of two anatomically distinct pathways for forward and retrograde conduction. Recent clinical

TABLE *Data on 13 patients with retrograde conduction*

| | | *QRS complex* | | *His bundle study* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *No.* | *Age, sex* | *Shape in V1* | *Duration* | *Site of block* | *PP* | *RR* | *AH* | *HV* | *Pacing cycle length* | *VA* | *VH′* | *HA* |
| 1 | 60 M | RBBB | 160 | Distal | 700 | 1800 | 85 | — | 780<br>520 | 160<br>B | — | — |
| 2 | 65 F | Normal | 100 | Proximal | 800 | 1370 | — | 30 | 770<br>520 | 260<br>B | — | — |
| 3 | 77 M | RBBB | 190 | Distal | 770 | 1700 | 90 | — | 720<br>580 | 260<br>B | — | — |
| 4 | 68 M | RBBB | 200 | Distal | 600 | 1920 | 80 | — | 560–520<br>440 | 140-160<br>B | — | — |
| 5 | 74 F | RBBB | 170 | Distal | 510 | 1620 | 65 | — | 480–400<br>340 | 160–200<br>B | 80–80 | 80–120 |
| 6 | 71 F | LBBB | 150 | Distal | 570 | 1500 | 55 | — | 550–300 | 180–200 | 150–160 | 30–40 |
| 7 | 79 M | RBBB | 140 | Distal | 740 | 900 | 100 | — | 760–400<br>345 | 120–180<br>B | 85–85 | 50–95 |
| 8 | 85 M | LBBB | 150 | Distal | 620 | 1200 | 70 | — | 710–360 | 130–200 | 80–80 | 50–120 |
| 9 | 75 M | LBBB | 180 | Distal | 760 | 1880 | 70 | — | 760–380 | ? | — | — |
| 10 | 65 M | RBBB | 200 | Distal | 750 | 1810 | 180 | — | 1090–630 | 180-180 | — | — |
| 11 | 59 F | LBBB | 180 | Distal | 650 | 1580 | 110 | — | 720–450<br>420 | 140–220<br>B | — | — |
| 12 | 65 F | LBBB | 140 | Distal | 640 | 1150 | 140 | — | 620–350<br>340 | 90–150<br>B | — | — |
| 13 | 66 M | RBBB | 150 | Distal | 660 | 2120 | 105 | — | 630<br>560 | 220<br>B | 75 | 145 |

Abbreviations: VA: ventriculoatrial time; RBBB: right bundle-branch block; LBBB: left bundle-branch block; B: block; all measurements are in ms.

FIG. 1 *Case 1 (see Table). Complete block and ventricular escape rhythm with prolonged QRS complexes. The site of the block is distal to the His bundle potential (upper tracing). Ventricular stimulation produces 1:1 VA conduction (lower tracing). BAE: bipolar right atrial electrogram. HBE: His bundle electrogram. S: stimulation artefact. H: His bundle activity.*

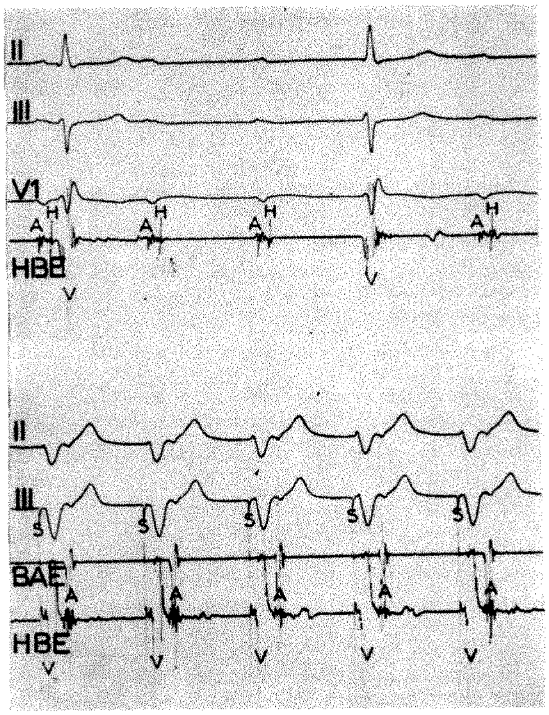
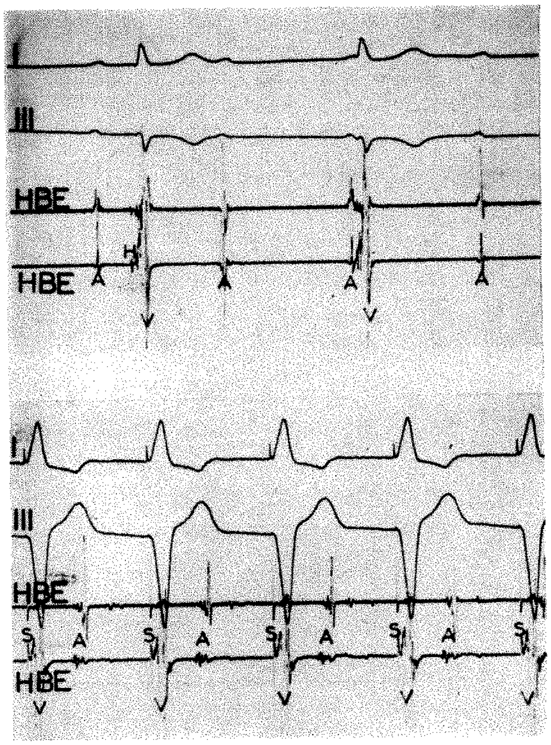


FIG. 2 *Case 2 (see Table): Complete AV block and ventricular escape rhythm with narrow QRS complexes. The AV conduction is interrupted proximal to the His bundle activity (upper tracing). Ventricular pacing is followed by retrograde conduction to the atria (lower tracing).*



observations support this (Gupta and Haft, 1972; Coumel *et al.*, 1973; Narula, 1974). However, an asymmetrical block could also be assumed in a damaged area of the specialized AV tissue, allowing conduction to occur in one direction but not in the other. Experimental studies by Mines (1913) and Ashman and Hafkesbring (1929) supported this hypothesis. Recordings of transmembrane potentials using microelectrodes have indicated unidirectional block in preparations of Purkinje fibres locally depressed by high concentrations of extracellular potassium (Cranefield, Klein, and Hoffman, 1971).

Although the occurrence of VA responses depends to a large extent on the lesions of the specialized pathways, other factors are implied in making the retrograde conduction manifest. Thus, a slow sinus rhythm increases the chances that a ventricular impulse will reach the atria during the phase of excitability. Conversely, the shortness of the sinus cycle length may prevent any retrograde depolarization. In our study the values of the PP control intervals were similar in patients with or without retrograde conduction, which minimizes the role of this factor in the results.

Likewise, the functional properties of the specialized tissue located proximal to the AV block

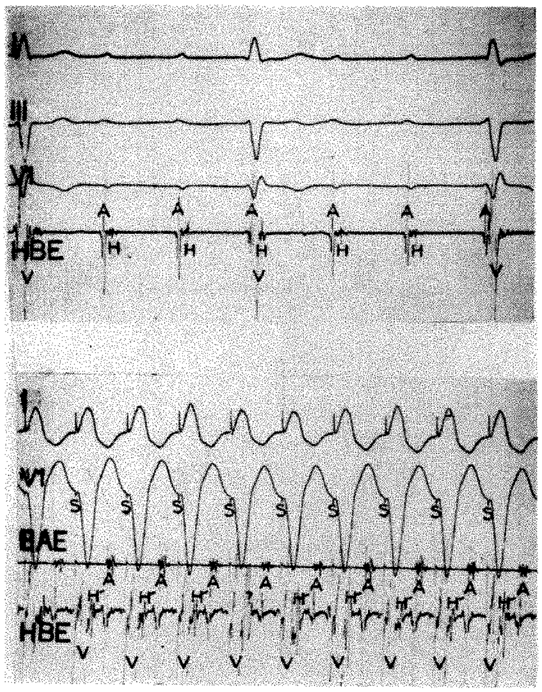
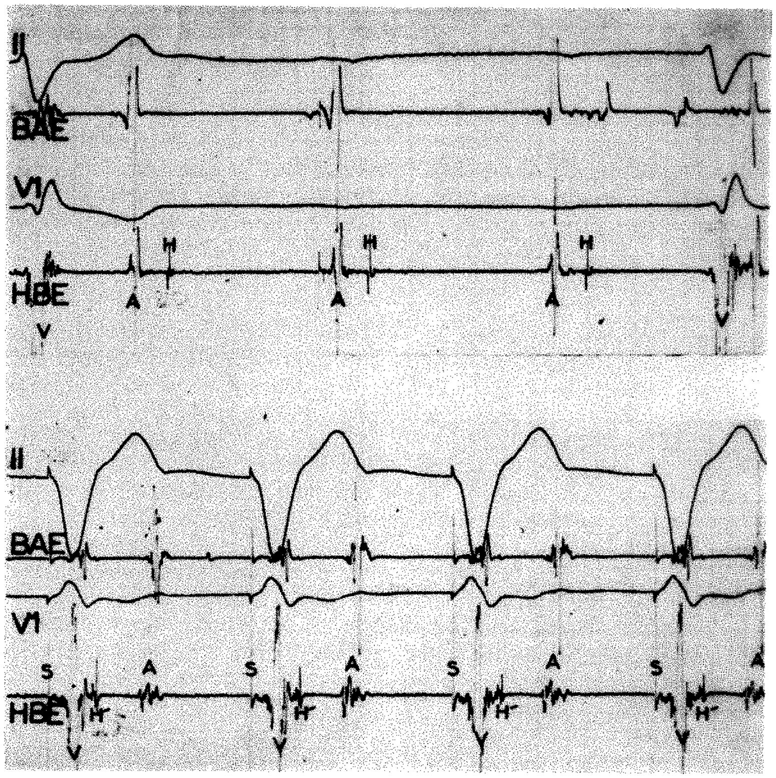


FIG. 3 *Case 7 (see Table): Complete AV block distal to H (upper tracing). Ventricular stimulation causes VA conduction. A retrograde His bundle potential (H') is apparent after the paced QRS complexes (lower tracing).*

FIG. 4 *Case 13 (see Table): Complete AV block distal to H (upper tracing). Ventricular pacing is followed by 1:1 VA conduction. An H' deflection can be identified after each QRS complex (lower tracing).*



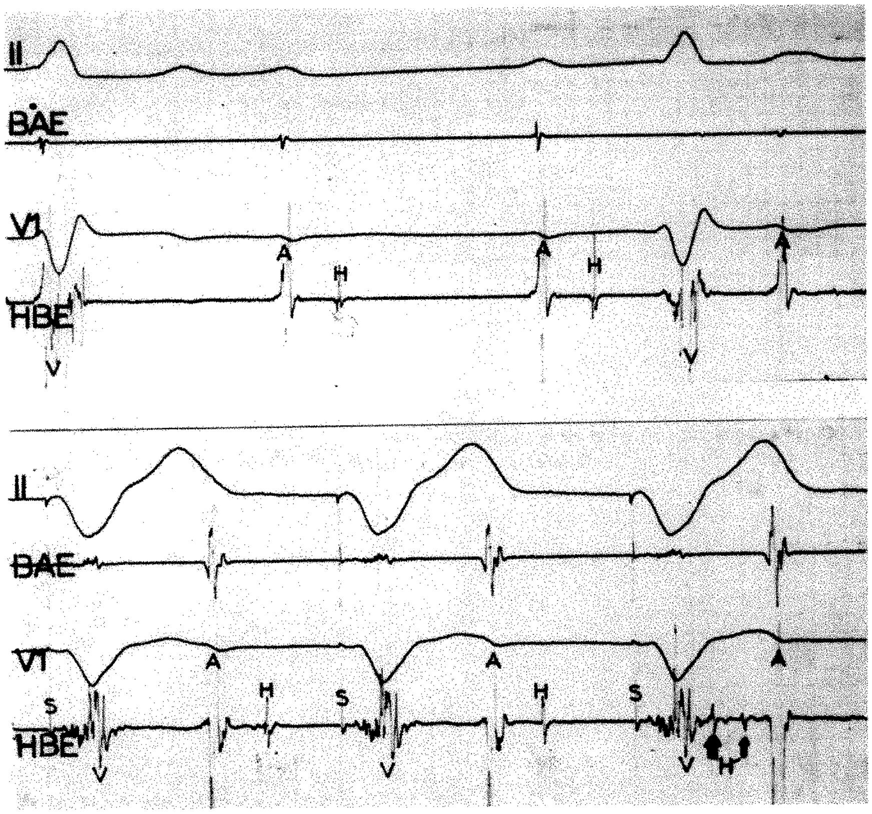


FIG. 5 *Complete AV block distal to H (upper tracing). Ventricular stimulation is accompanied by AV dissociation (lower tracing). In the first two ventricular beats retrograde block is infra-Hisian. On the other hand the third beat is followed by a split His bundle potential (indicated by an arrow) suggesting impaired retrograde conduction within the common bundle. The concealed excitation dies within the AV node. A refractory state then ensues which is responsible for the AV nodal block of the following atrial beat: H disappears.*

can be important. The AV node has a long refractory period and the safety margin for the impulse conduction is low. The influence of the preceding AV node depolarization on the retrograde conduction of the following ventricular beat explains the relation sometimes seen between the PR interval and the RP retrograde conduction interval. The shortening of the PR interval is accompanied by a lengthening of the VA delay, and vice versa (Wolferth and McMillan, 1929; Winternitz and Langendorf, 1944). In a study using His bundle recordings and ventricular pacing, Narula and Samet (1970) stressed the role of the AV node in the genesis of retrograde block. According to them the sites of AV and VA block are not necesssarily the same. Retrograde impulse may block within the AV node, whereas the anatomical lesions are infra-Hisian. The present work has shown that in most cases of complete heart block antegrade and retrograde block occur at the same level. The retrograde excitation occasionally reached the AV node, where it was extinguished in only two patients with an AV block distal to H. This concealed conduction was revealed by its after-effects on the transmission of the following sinus impulse: lengthening of AH in one case, and disappearance of H in the other after recording of a retrograde His bundle potential (Fig. 5). Similar phenomena were previously reported by others (Puech *et al.*, 1974; Cohen *et al.*, 1974; Takeshita, Tanaka, and Nakamura, 1974).

The ventricular rate also plays an important role in the occurrence of retrograde conduction to the atria. In our 13 cases electrical stimulation of the ventricles induced a VA response at a rate above the sinus rate. However, 5 of them showed intermittent VA conduction during spontaneous rhythm. If these findings are related to the site of the AV lesions unidirectional block was mainly found in cases with distal lesions of the His-Purkinje system. On the other hand, the main bundle blocks were bidirectional. Similar observations were made by Narula and Samet (1970).

During VA conduction the His bundle potential was usually buried in the QRS complex, except in 5 cases where it was visible. One patient showed a VA delay which affected the VH′ interval (150 to 160 ms) but not the retrograde AV nodal conduction time (H′A interval) (Table—Case 6). In the other cases the AV node was the main determinant of the retrograde delay inducing the rate-dependent increase in the VA time, then the impulse block. The participation of the AV node-His pathway in the retrograde conduction can also be shown by the use of pharmacological agents. Atropine and isoprenaline cause shortening of the VA time (Takeshita *et al.*, 1974), whereas retrograde conduction is blocked by vagomimetic drugs (Puech *et al.*, 1970b).

Finally, the mechanism of VA transmission is still not clearly understood. No definite conclusion arises from the present data. Unidirectional block in the damaged specialized area may be operative. However, the presence of Mahaim fibres bypassing the block area and functioning only in retrograde manner cannot be excluded.

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# Echocardiographic findings after acute carbon monoxide poisoning[1]

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*Myocardial lesions are frequently seen at necropsy after fatal carbon monoxide poisoning. Clinically, while there have been numerous reports of chest pain and electrocardiographic changes associated with acute carbon monoxide poisoning, other evidence for left ventricular abnormality has not been reported. The echocardiographic findings in five cases of non-fatal poisoning are presented here. Abnormal left ventricular wall motion was shown by echocardiography in 3 cases. Motion returned to normal in 2 of the 3 in follow-up tracings. Echocardiograms on 3 of the 5 patients showed mitral valve prolapse. Though the mitral valve prolapse may have been present before the poisoning, the reported high incidence of papillary muscle lesions in fatal cases suggests a possible relation of the prolapse to the effects of the carbon monoxide poisoning.*

Myocardial damage, including necrosis, is commonly seen at necropsy after fatal carbon monoxide poisoning (Marek and Piejko, 1972; Gey, 1924; Ehrich, Bellet, and Lewey, 1944; Beck, Schulze, and Suter, 1940). It has also been shown in experimental animals who were sacrificed after non-fatal poisoning (Ehrich *et al.*, 1944). The subendocardial and papillary muscle areas of the left ventricle are most frequently involved (Marek and Piejko, 1972; Gey, 1924; Ehrich *et al.*, 1944). The lesions resemble those caused by severe hypoxia (Marek and Piejko, 1972) which carbon monoxide may produce by two mechanisms: (1) by replacing the oxygen in oxyhaemoglobin, and (2) by decreasing the dissociation of oxyhaemoglobin in the tissues (Ayres, Gianelli, and Mueller, 1970; Goldsmith and Landaw, 1968; Hayes and Hall, 1964).

Electrocardiographic abnormalities are often seen after carbon monoxide poisoning (Hayes and Hall, 1964; Anderson, Allensworth, and DeGroot, 1967; Leinoff, 1942; Hadley, 1952; Cosby and Bergeron, 1963; Middleton, Ashby, and Clark, 1961; Meigs and Hughes, 1952; Stearns, Drinker, and Shaughnessy, 1938; Colvin, 1928). These are usually transitory but may persist for days or weeks (Cosby and Bergeron, 1963; Middleton *et al.*, 1961). The most common changes are sinus tachycardia, T wave flattening or inversion, and ST segment depression (Ehrich *et al.*, 1944; Cosby and Bergeron, 1963; Meigs and Hughes, 1952; Stearns *et al.*, 1938). Premature ventricular complexes (Meigs and Hughes, 1952; Stearns *et al.*, 1938), atrial fibrillation (Cosby and Bergeron, 1963; Meigs and Hughes, 1952; Stearns *et al.*, 1938), and low voltage (Stearns *et al.*, 1938) occur less frequently. ST segment elevation has occasionally been recorded (Hayes and Hall, 1964; Leinoff, 1942; Stearns *et al.*, 1938) as have conduction abnormalities (Stearns *et al.*, 1938; Colvin, 1928).

This report describes the echocardiographic findings in 5 patients who were poisoned on the same day by carbon monoxide from a defective water heater in an apartment building. The gas reached the apartments through the air conditioning ducts. The duration of the exposure is unknown. All 5 patients had been in good health before the accident.

## Methods

Each patient had at least one echocardiogram during his time in the hospital. Follow-up echocardiograms were obtained 2 to 10 months after discharge.

Echocardiography was performed with a Smith Kline echograph and either a Honeywell No. 1856

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or an Electronics for Medicine DR8 strip chart recorder. The ultrasound transducer was 1·27 cm in diameter and collimated at 7·5 cm.

A sector scan of the left ventricle from base to apex (Feigenbaum, 1972) was made in each examination and the following measurements were made where echoes were simultaneously recorded from the left side of the interventricular septum, the posterior left ventricular endocardium, and either the posterior leaflet or the chordae tendineae of the mitral valve: (1) the left ventricular internal dimension at end-diastole (LVIDd); (2) amplitude of motion of the left septal echo during ejection (LSa); and (3) amplitude of motion of the posterior left ventricular endocardial echo. Pattern of motion of the mitral valve and of the interventricular

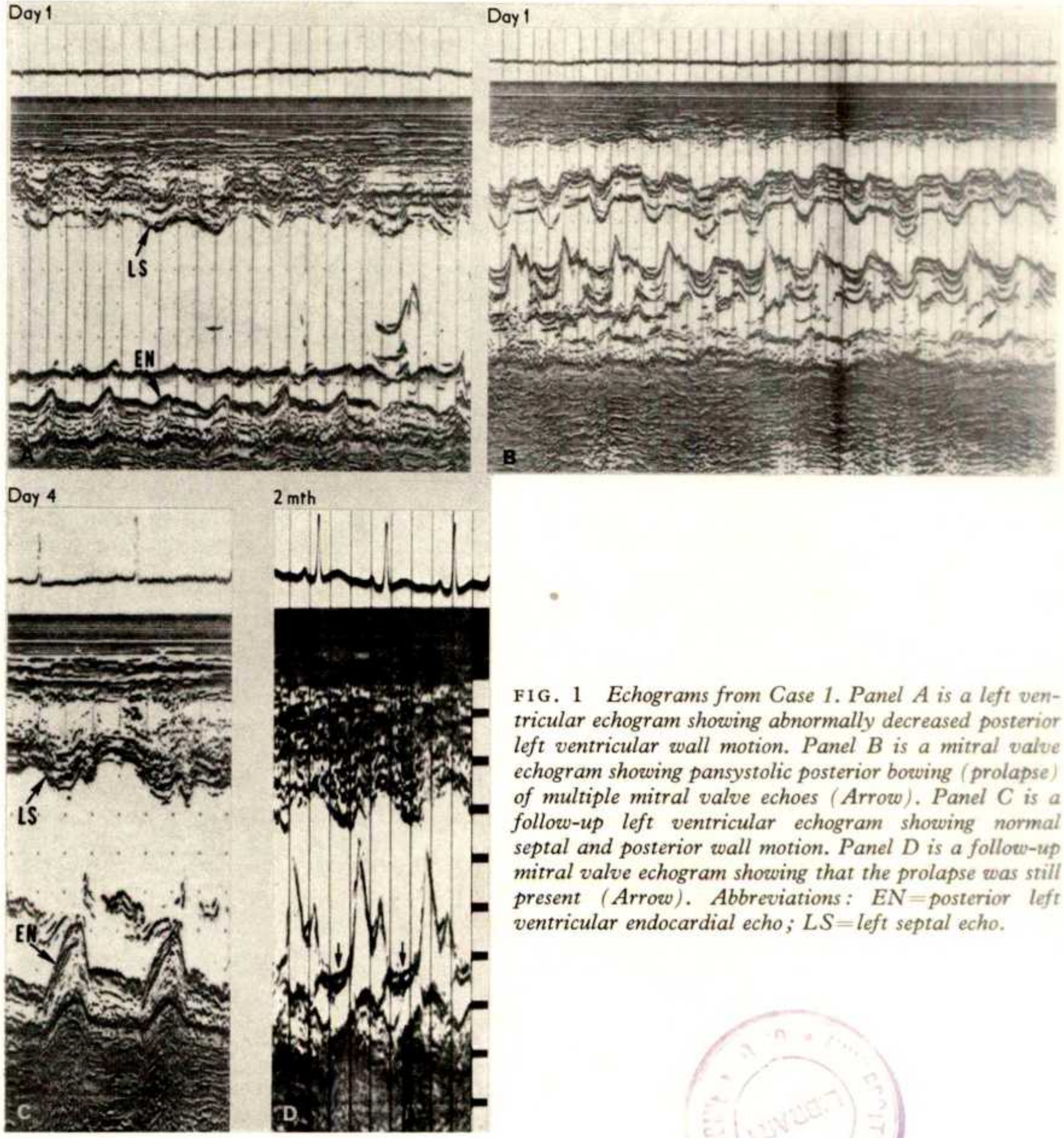

FIG. 1 *Echograms from Case 1. Panel A is a left ventricular echogram showing abnormally decreased posterior left ventricular wall motion. Panel B is a mitral valve echogram showing pansystolic posterior bowing (prolapse) of multiple mitral valve echoes (Arrow). Panel C is a follow-up left ventricular echogram showing normal septal and posterior wall motion. Panel D is a follow-up mitral valve echogram showing that the prolapse was still present (Arrow). Abbreviations: EN=posterior left ventricular endocardial echo; LS=left septal echo.*

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septum and posterior left ventricular wall near the apex was also noted. Patients were not examined by the authors and phonocardiograms were not obtained.

## Case reports

### Case 1

This 16-year-old man was comatose on admission with a heart rate of 130 beats a minute, a respiratory rate of 26 cycles a minute, a blood pressure of 100/70 mmHg (13·3/9·3 kPa), and body temperature of 37·8°C. While receiving 100 per cent $O_2$ his arterial $Po_2$ was 150 mmHg (20·0 kPa) with a $Pco_2$ of 26 mmHg (3·5 kPa) and a *p*H of 7·24. His carbon monoxide level was 25 per cent on admission.

At the time of admission, his echocardiogram showed abnormally low amplitude of motion of the posterior endocardial echo and prolapse of the mitral valve throughout systole. The left ventricular internal dimension was 5·6 cm. These findings are illustrated in Fig. 1A and Fig. 1B. A repeat echocardiogram on day four showed normal septal and posterior left ventricular wall motion (Fig. 1C). A follow-up echo two months later was normal except for the mitral valve prolapse (Fig. 1D). The left ventricular internal dimension at end-diastole on that tracing was 4·7 cm.

### Case 2

The brother of the patient in Case 1 was a 20-year-old man who was semicomatose on admission. He had bilateral Babinski signs and intermittent decerebrate posturing. His heart rate was 120 beats per minute and regular, blood pressure was 170/100 mmHg (22·6/13·3 kPa), respiratory rate was 40 per minute, and temperature was 39·4°C. The carbon monoxide level was 23 per cent.

On day two he could respond to simple commands; and heart rate, respiration rate, and blood

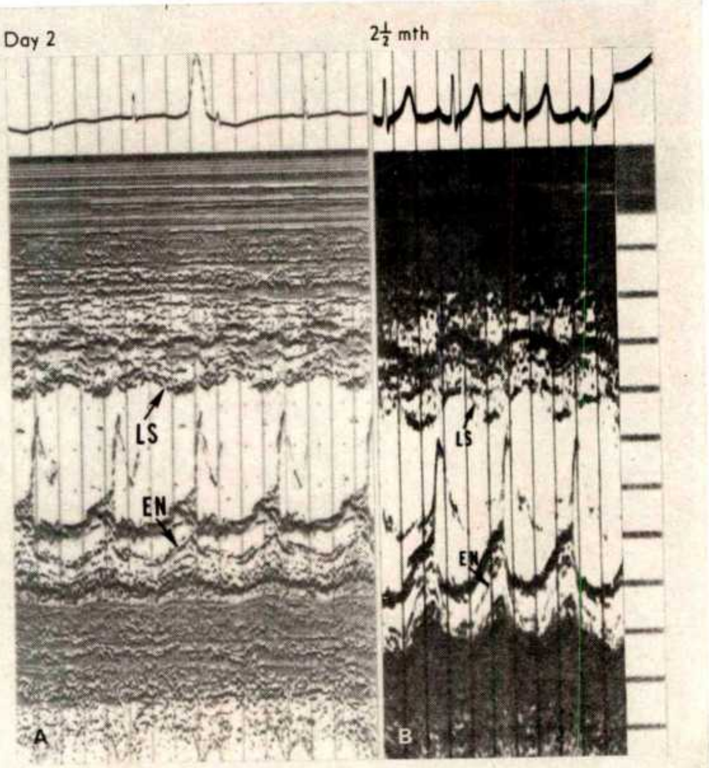

FIG. 2 *Left ventricular echograms from Case 3. In panel A the posterior left ventricular wall motion is abnormally decreased. Panel B is a follow-up echogram showing that the motion did return to normal. Abbreviations: EN = posterior left ventricular endocardial echo; LS = left septal echo.*

pressure were normal. The echocardiogram on day two showed posterior bowing of multiple mitral valve echoes during systole. On day four he was alert and had no complaints. An echocardiogram on day four showed slight increase in the left septal and posterior left ventricular wall motion as compared with the first tracing. An echocardiogram 3½ months later was unchanged.

### Case 3

This 20-year-old woman was stuporous on admission. Her heart rate was 132 beats per minute, blood pressure was 130/90 mmHg (17·3/12·0 kPa), respiratory rate was 30 per minute, and temperature was 37°C. On 100 per cent $O_2$ by mask, her arterial $Po_2$ was 108 mmHg (14·4 kPa). The carbon monoxide level was 17 per cent. On day two she was on room air and the arterial $Po_2$ was 82 mmHg (10·9 kPa). Heart rate was 76 beats per minute. Her echocardiogram showed a normal size left ventricle and normal mitral valve motion. The amplitude of motion of the posterior left ventricular endocardium was less than normal as shown in Fig. 2A. She was released on day three.

An echocardiogram 2½ months later showed normal left ventricular size and wall motion (Fig. 2B) and mid-systolic prolapse of the mitral valve.

### Case 4

A 24-year-old woman had been unconscious when found but was only confused on admission. She complained of dizziness and mild headache. Her heart rate was 128 beats per minute, respiratory rate was 24 per minute, blood pressure was 120/80 mmHg (16·0/10·6 kPa), and temperature was 37·6°C. On 100 per cent $O_2$ by mask, arterial $Po_2$ was 175 mmHg (23·3 kPa). The carbon monoxide level was 19 per cent.

Her echocardiogram was normal though the amplitude of the posterior endocardial echo motion was at the lower limit of normal.

On day three she was asymptomatic and was discharged from the hospital.

A follow-up echocardiogram 2½ months later was normal.

### Case 5

A 29-year-old man was disorientated and aggressive on admission. His heart rate was 140 beats per minute and regular respiratory rate was 36 per minute, blood pressure was 154/95 mmHg (20·5/12·6 kPa), and temperature was 38·5°C. The carbon monoxide level was 16 per cent. After one and a half hours of 100 per cent $O_2$ therapy by mask, he was orientated and co-operative and his arterial $Po_2$ was 250 mmHg (33·3 kPa).

The first echocardiogram on this patient was taken on day seven and showed a normal LVIDd, decreased septal motion at the base (Fig. 3A), with paradoxical septal motion near the apex (Fig. 3B). The amplitude of the left ventricular posterior wall motion was at the upper limits of normal.

An echocardiogram obtained 10 months later continued to show abnormal septal motion.

The echocardiographic findings for all 5 patients are summarized in the Table.

## Discussion

After acute carbon monoxide poisoning, 4 of the 5 patients had echocardiographic abnormalities. While these observations do not establish that

TABLE *Echocardiographic findings*

| *Case No.* | *Hospital day and follow-up* | *LVIDd (cm)* | *LSa (cm) (N=0·2–0·8 cm)* | *ENa (cm) (N=0·8–1·6 cm)* | *Mitral valve* |
|---|---|---|---|---|---|
| 1 | 1 | 5·6 | 0·4 | 0·6 | Prolapse |
| | 4 | 5·6 | 0·6 | 1·7 | Prolapse |
| | 2 mth | 4·7 | 0·7 | 1·4 | Prolapse |
| 2 | 2 | 4·8 | 0·6 | 1·2 | Prolapse |
| | 4 | 4·8 | 0·8 | 1·3 | Prolapse |
| | 3½ mth | 4·5 | 0·7 | 1·3 | Prolapse |
| 3 | 2 | 4·4 | 0·3 | 0·6 | Normal |
| | 2½ mth | 4·6 | 0·6 | 1·3 | Prolapse |
| 4 | 2 | 4·5 | 0·6 | 0·9 | Normal |
| | 2½ mth | 4·7 | 0·6 | 1·0 | Normal |
| 5 | 7 | 4·7 | 0 | 1·6 | Normal |
| | 10 mth | 4·7 | 0 | 1·4 | Normal |

LVIDd=left ventricular internal dimension at end-diastole; LSa=amplitude of left septal motion during ejection; ENa=amplitude of posterior left ventricular endocardial echo motion.

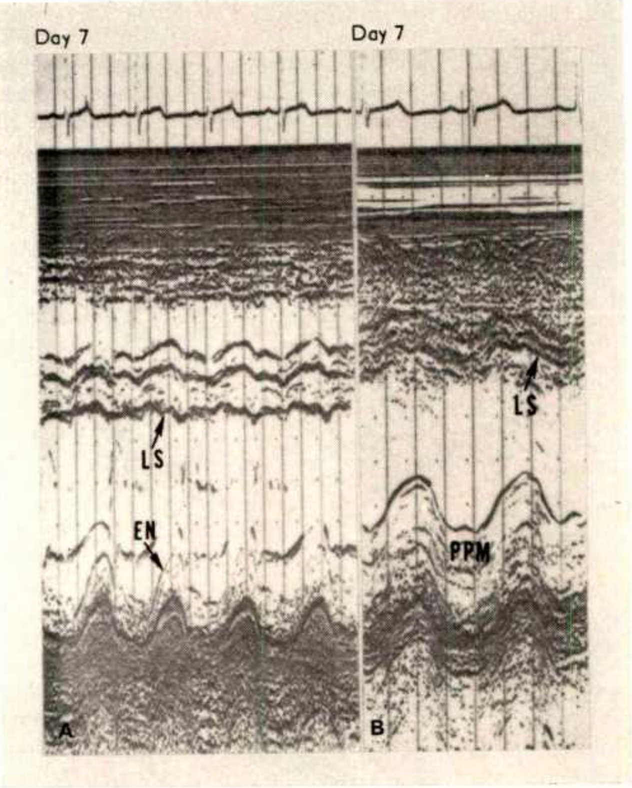

FIG. 3 *Left ventricular echograms from Case 5. Panel A shows absence of left septal echo motion during ejection near the base of the ventricle. Panel B shows paradoxical left septal echo motion in an area at the level of the posterior papillary muscle (PPM). Abbreviations: EN=posterior left ventricular endocardial echo; LS=left septal echo.*

carbon monoxide was the cause of the abnormalities or that its mechanism of action was myocardial oxygen deprivation, pre-existing cardiac disease is unlikely since all 5 patients were previously in good health and under 30 years of age.

## Echocardiograms

**Left ventricular internal dimension** The left ventricular internal dimension at end-diastole (LVIDd) was normal in every echocardiogram when the body surface area was considered. In Case 1 the LVIDd decreased from 5·6 cm on the first hospital day to 4·7 cm on a follow-up tracing two months later. While this is a significant change and suggestive of improved left ventricular function, both values are normal and the difference could be the result of physiological variation.

Echocardiographic ejection fractions were not calculated in these cases since their reliability depends on symmetrical contraction and, at least in Case 5, segmental abnormality of contraction was present with the septal motion paradoxical and with the amplitude of posterior left ventricular wall motion at the upper limit of normal.

**Left ventricular wall motion** Abnormalities of left ventricular echo motion have been shown in patients with cardiomyopathy (Corya *et al.*, 1974; McDonald, 1973) and in patients with obstructive coronary artery disease (Jacobs *et al.*, 1973; Corya *et al.*, 1975; Ratshin, Rackley, and Russell, 1972; Heikkilä and Nieminen, 1975). It may occur transiently during spontaneous or stress induced angina pectoris (Jacobs *et al.*, 1973; Widlansky *et al.*, 1975). Though the finding is non-specific, it probably is the result of myocardial hypoxia in these cases of carbon monoxide poisoning. In Cases 1 and 3 the motion returned to normal when the echocardiogram was repeated. In Case 5 the abnormal septal motion was still present 10 months later.

## Mitral valve prolapse

There have been numerous reports showing excellent correlation between echocardiographic and angiocardiographic findings of mitral valve prolapse in patients with a variety of auscultatory and phonocardiographic findings (Dillon *et al.*, 1971; Popp *et al.*, 1974; DeMaria *et al.*, 1974). The posterior motion of the mitral valve leaflets may begin very early in systole, giving the echo a bowed or hammock appearance, or it may begin abruptly in mid-systole (Popp *et al.*, 1974; DeMaria *et al.*, 1974; Shah and Gramiak, 1970). Mitral valve prolapse has become a common echocardiographic finding (Popp *et al.*, 1974; DeMaria *et al.*, 1974) and both the aetiology and the clinical significance of it are undetermined. Because previous echocardiograms were not available it is uncertain that carbon monoxide was responsible for prolapse in our three cases. None of the patients had physical findings suggesting Marfan's syndrome or other congenital abnormalities. Since 2 of the 3 patients were brothers, a familial disorder cannot be ruled out as the aetiology in those cases. However, in view of the known frequency of papillary muscle lesions in patients who die with carbon monoxide poisoning (Marek and Piejko, 1972; Gey, 1924), papillary muscle dysfunction must be considered a likely cause of the prolapse in these cases.

## Conclusion

These echocardiographic observations suggest that myocardial injury may occur in non-fatal cases of carbon monoxide poisoning. The damage, as shown by abnormal left ventricular echo motion, is reversible in some cases; and mitral valve prolapse may result from papillary muscle involvement.

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# Non-ejection systolic clicks and mitral systolic murmurs in Black schoolchildren of Soweto, Johannesburg[1]

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*A survey was conducted on 12 050 Black schoolchildren, aged 2 to 18 years, in the South Western Townships of Johannesburg (Soweto), and the prevalence of non-ejection systolic clicks and late systolic murmurs was determined. One or both of these auscultatory findings were detected in 168 children, yielding a prevalence rate of 13·99 per 1000 in the school population. A female preponderance of 1·9:1 was present and there was a strong linear increase in prevalence with age, with a peak rate of 29·41 per 1000 in 17-year-old children. A non-ejection click was the only abnormal auscultatory finding in 123 children (73%) and a mitral systolic murmur in 8 (5%), whereas in 37 (22%) both these findings were present. Of the latter 37 children, the murmur was late systolic in 32; in 5 it was early systolic. Auscultation in different postures was important in the detection of both non-ejection clicks and mitral systolic murmurs. Experience in the detection of these auscultatory findings influenced the frequency with which they were heard. Electrocardiographic abnormalities compatible with those previously described in the billowing mitral leaflet syndrome were present in 11 of 158 children.*

*The aetiology of these auscultatory findings in this community remains unknown. In the same survey, a high prevalence rate of rheumatic heart disease was recorded and the epidemiology of the non-ejection clicks and these mitral systolic murmurs showed similarities to that of rheumatic heart disease. Though the specific billowing mitral leaflet syndrome almost certainly accounts for some of these auscultatory findings, a significant proportion may have early rheumatic heart disease. Further elucidation of this problem is necessary.*

A non-ejection systolic click, late systolic murmur, or both, are attributed to billowing of the mitral leaflets, especially the posterior one. Since the possibility of a mitral valve origin for these auscultatory findings was revived by Reid (1961), there have been numerous publications on different aspects of this somewhat complex entity. These include clinical (Barlow *et al.*, 1968; Jeresaty, 1973; Cobbs, 1974; Barlow and Pocock, 1975), aetiological (Pocock and Barlow, 1971; Barlow and Pocock, 1975), and familial (Barlow, 1965; Hancock and Cohn, 1966; Shell *et al.*, 1969) studies as well as an analysis of angiocardiographic (Criley *et al.*, 1966; Grossman *et al.*, 1968), electrocardiographic (Pocock and Barlow, 1971; Jeresaty, 1973; Barlow and Pocock, 1975), echocardiographic (Popp *et al.*, 1974), and pathological (Shappell *et al.*, 1973; Barlow and Pocock, 1975) manifestations. Considerable further interest has been stimulated by the recognition of an association with arrhythmias (Hancock and Cohn, 1966; Pocock and Barlow, 1970; Barlow and Pocock, 1975) or conduction defects (Gulotta *et al.*, 1974; Barlow and Pocock, 1975), and the predisposition to the development of infective endocarditis (Linhart and Taylor, 1966; Barlow *et al.*, 1968; Lachman *et al.*, 1975). Despite the wealth of literature, the prevalence and, there-

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fore, the significance of these features in the general population have not yet been ascertained. Only one population survey has been published and this was in Bari, Italy (Rizzon *et al.*, 1973), where 1009 young adult women were auscultated and a non-ejection systolic click, late systolic murmur, or both were detected in 3·3 per 1000. In previous communications from this laboratory (Barlow *et al.*, 1968; Pocock and Barlow, 1971), these auscultatory signs were reported in 220 patients, 210 of whom were White. Subsequently, we have encountered more than 200 additional White patients, most of whom were referred to this Unit for elucidation of their abnormal auscultatory findings or electrocardiograms or because of symptoms such as chest pain, palpitation, and syncope (Barlow and Pocock, 1975). The prevalence in the general population cannot be determined from these numbers, and variations with age, ethnic group, and geographical site are also unknown.

In 1972, a cardiological survey was undertaken on schoolchildren of the South Western Townships (Soweto) for Blacks, near Johannesburg, with the primary objective of determining the prevalence of rheumatic heart disease in that population (McLaren *et al.*, 1975). The survey also provided an opportunity for finding out the prevalence of non-ejection systolic clicks with or without mitral systolic murmurs.

## Subjects and methods

A total of 12 050 children were randomly selected from 58 primary schools and 32 crèches in Soweto to represent a total Black school population of about 99 000. The method of sampling has been previously described (McLaren *et al.*, 1975) and was based on a stratified technique, in which the population was divided into 3 strata according to educational level—crèche children (2 to 6 years old), lower primary schoolchildren (first 4 school years), and higher primary schoolchildren (fifth to eighth school years). An age range of 2 to 18 years was thus obtained and the sex distribution was equal.

The children were examined by a team of 10 doctors, 5 of whom were experienced cardiologists and the remainder had all received at least 6 months training in this Unit. Three observers were present at each session and at least one of them was a senior cardiologist. Auscultation was performed on all children in the supine and left lateral positions. A random 10 per cent of children were also examined in the erect and squatting postures, as were those in whom the cardiac findings necessitated further elucidation, such as in children with a non-ejection systolic click, late systolic murmur, or an arrhythmia. Children with normal hearts were examined by one observer only, but when an abnormal heart was suspected or detected, the child was then 'recirculated' to the other 2 observers who were unaware that the child had already been examined. Initially, the children with non-ejection clicks or late systolic murmurs were likewise 'recirculated', but this practice was soon abandoned when it became apparent that these findings were common and that their often transient nature sometimes led to their temporary disappearance when the children were later re-examined. However, the presence of either a non-ejection click or a late systolic murmur had to be confirmed by at least one of the other 2 observers. Electrocardiograms and blood pressure determinations were recorded on children with abnormal hearts and on those routinely postured.

The age, sex, home, and school areas of the children as well as family size, as assessed by the number of sibs, were documented. The educational grades of the children were also noted because, despite some correlation with age, there is a considerable age variation in each grade. Though ethnic group was recorded, this factor is of doubtful significance in this urban community in which the inhabitants represent many different Black ethnic groups but are differentiated to a large extent by language only. Other observations included a clinical and anthropometric nutritional assessment and the carrier rate of Lancefield's Group A beta-haemolytic streptococcus in the throat. Statistical analysis was based on two techniques, a $\chi^2$ test for nominal data and an unpaired Student's t test for all interval data.

## Results

### Prevalence

A non-ejection click, a late systolic murmur, or both, were detected in 168 children, yielding an overall prevalence rate in the sample school population of 13·99 per 1000. The optimally weighted estimate of the prevalence in the total school population (Cochran, 1963; McLaren *et al.*, 1975) was 13·42 per 1000 with a 95 per cent confidence interval of ±2·1. Three children were considered (McLaren *et al.*, 1975) to have established rheumatic heart disease with associated non-ejection clicks and are not included in the 168. The prevalence rate in crèche children was 5·26 per 1000 while in the lower primary and higher primary schoolchildren it was 11·84 and 17·76 per 1000, respectively.

Of the 168 children with these auscultatory

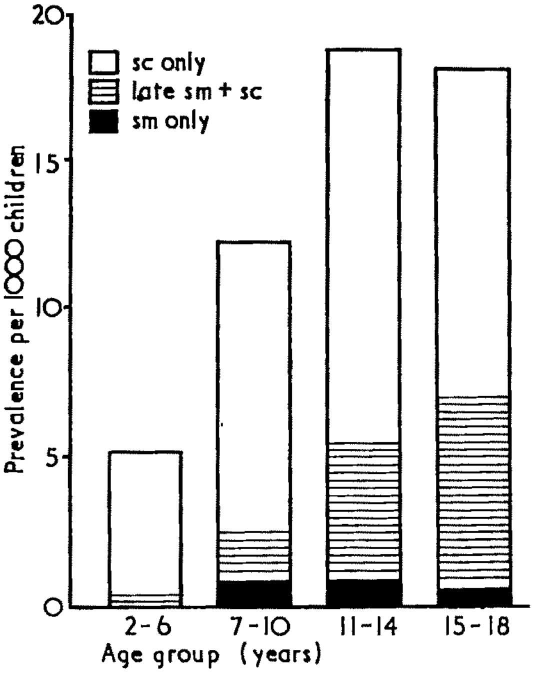

FIG. 1 *Varying prevalence of non-ejection systolic clicks (SC), late systolic murmurs (late SM), or both (late SM+SC) with age. There is a linear association (P< 0·001).*

findings, 32 had been routinely postured and the prevalence rate for this group (1174 children) was 27·3 per 1000. If the children examined by the less experienced observers are excluded from the sample, then the overall prevalence is increased to 19·2 per 1000.

### Epidemiological factors

The sex ratio showed a female preponderance of 1·9:1. A strong linear association ($P < 0{\cdot}001$; Fig. 1) between age and prevalence was present (a test for non-linearity was not significant, $\chi^2 = 16{\cdot}41$, $P > 0{\cdot}05$). The youngest age recorded was 3 years (3 children with isolated non-ejection clicks) and the maximal prevalence rate of 29·41 per 1000 occurred in children aged 17 years. If the individual school grades are considered (Fig. 2), the peak prevalence rate was recorded in the seventh and eighth school grades ($P < 0{\cdot}01$).

There was no significant correlation between prevalence and family size, ethnic group, home area, or school area ($P > 0{\cdot}05$).

Throat cultures were carried out in all but 6 of the 168 children. The carrier rate of Lancefield's Group A beta-haemolytic streptococcus was 61·7 per 1000 but this is not significantly greater ($P > 0{\cdot}05$) than the carrier rate in the children with normal hearts (52 per 1000).

The nutritional status of children with non-ejection clicks with or without mitral systolic murmurs was assessed clinically as average in 82 per cent, undernourished in 14 per cent, and unusually well-nourished or obese in 4 per cent. In children with normal hearts, these figures were 86, 7, and 7 per cent respectively.

### Auscultatory features

A non-ejection click only was heard in 123 children (73%), an isolated mitral systolic murmur in 8 (5%), and both these auscultatory findings in 37 (22%).

### Non-ejection systolic clicks

A non-ejection systolic click was the commonest abnormal auscultatory finding and was detected in 160 children or 13·3 per 1000 of the school population. It was loudest at the left parasternal border in 74 children (46%), over the cardiac apex in 60 (38%), and at both these sites in 26 (16%). In 86 children (54%) the click was present intermittently.

The click was audible in all postures in 57 per cent of children. In 84 per cent it was heard in more than one posture and if present in only one posture this was most frequently the standing position (11%). In the supine position, 22 per cent of clicks were not heard and would thus have been missed if auscultation in the other postures had been omitted. The presence of extrasystoles in 2 children led to their being postured and a click was then detected on standing. In another 2 the click became audible on re-examination in the supine position after posturing.

### Mitral systolic murmurs

The diagnostic criteria for a 'mitral systolic murmur' in this group of children were either a late systolic murmur with or without a non-ejection click, or an apical early systolic murmur (Barlow and Pocock, 1975) provided this was associated with a non-ejection click. A mitral systolic murmur was present in 45 children (27%), yielding a prevalence rate for the school population of 4 per 1000. In 40 children the murmur was classified as late systolic and this was associated with a non-ejection click in all but 8. The remaining 5 children had an early systolic murmur and non-ejection click.

In the supine position 32 of the 45 murmurs were present and, with the exception of 2 murmurs of grade 3/6 intensity, all were grade 1 to 2. In one child the intensity of the murmur changed from grade 3 to grade 4 on standing and squatting.

The effect of posture on the length of the murmur

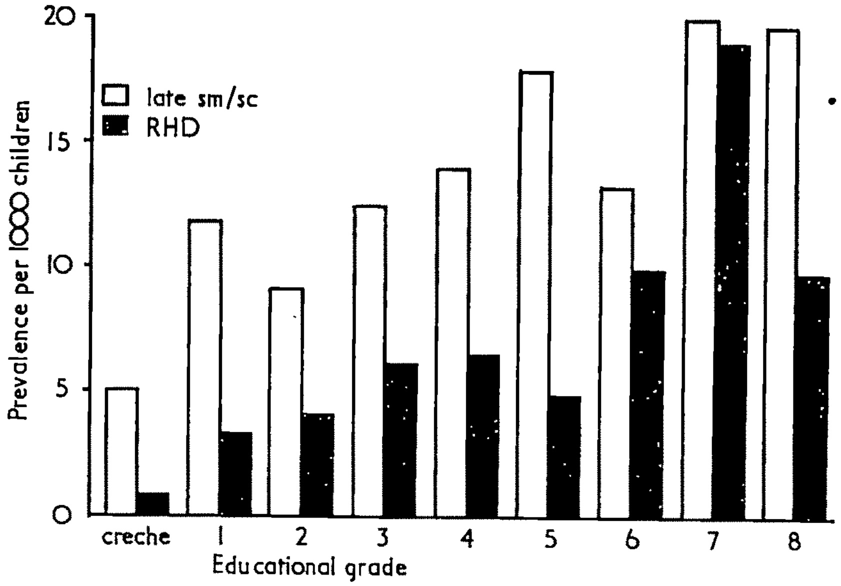

FIG. 2 *Association of prevalence of late systolic murmurs and/or non-ejection systolic clicks (late SM/SC), and rheumatic heart disease (RHD) with educational grade.*

was stated in 36 children only. In 4 children the murmur became pansystolic on standing. In 2 of them the murmur was late but long in the supine position and no non-ejection click was present, while in the other 2 the murmur was early systolic in the supine position and was associated with a non-ejection click. Of the early systolic murmurs detected in 3 further children, one was present in the supine position and became late systolic on standing and squatting, one was present in the supine and squatting positions and did not become late systolic, and one was audible in the standing position only. The mitral systolic murmur was absent in the supine position in 13 children. In 2 of them the murmur became audible in the left lateral position, whereas in the remainder it became apparent only when the child was examined in the standing position either routinely or because of the detection of a non-ejection click in the supine position.

### Physiological murmurs and third heart sounds

In addition to the above auscultatory findings, a vibratory systolic murmur or Still's murmur (Still, 1915) was present in 62 (37%) of the 168 children, which was less frequent than in the general school population. A physiological third heart sound was heard in 153 (91%), whereas the overall prevalence in the school population was 97 per cent.

### Blood pressure and electrocardiograms

The systolic and diastolic blood pressures did not differ from those of the control population.

Of the 158 children who had a technically satisfactory electrocardiogram, 11 (7%) had abnormalities compatible with those previously described in the billowing mitral leaflet syndrome (Hancock and Cohn, 1966; Pocock and Barlow, 1971; Jeresaty, 1973; Barlow and Pocock, 1975). Flattening or inversion of the T waves in the inferior leads (II, III, and aVF) and mid or lateral praecordial leads was present in 8 children, whereas 2 had inferior changes only and in the remaining child, a 14-year-old girl, inverted T waves were confined to the chest leads V1 to V5. A late systolic murmur was the abnormal auscultatory finding in 3 of these children and a non-ejection click in 5, while in 3 both findings were present.

## Discussion

The Soweto survey has revealed that non-ejection clicks and late systolic murmurs are common abnormal auscultatory findings in Black schoolchildren. The prevalence was highest in adolescent children of 11 to 18 years of age, but in all age-groups it was greater than that reported in young adult women of the Bari survey (Rizzon *et al.*, 1973). Certain other characteristics of these findings have been confirmed. There was a female preponderance and this has been reported (Barlow *et al.,* 1968; Jeresaty, 1973) in the billowing mitral leaflet syndrome. The importance of posture in the detection of non-ejection clicks and these mitral systolic murmurs (Fontana *et al.,* 1970; Cobbs, 1974; Lachman *et al.,* 1975) is further emphasized and auscultation in the standing position proved the most contributory. An early systolic murmur as detected in 5 children in this survey has previously been described (Cobbs, 1974; Barlow and Pocock, 1975). That awareness of these auscultatory findings and experience in their detection influence the frequency with which they are heard (Lachman *et al.,* 1975) was confirmed by the higher prevalence rate obtained by the more experienced observers.

Before the significance of the high prevalence of these auscultatory findings in this community can be assessed, it is necessary to examine some of the aetiological factors which may affect the complex mitral valve mechanism (Barlow and Pocock, 1975). At the outset, it is possible to exclude occlusive coronary artery disease because of its extreme rarity in this population group even in adults (Seftel, Kew, and Bersohn, 1970). There was no clinical evidence of hypertrophic obstructive cardiomyopathy, which is also extremely rare in South African Blacks (Tucker *et al.,* 1975), nor was there associated congenital heart disease, previous mitral valvotomy, or trauma. Congestive cardiomyopathy is prevalent in Southern Africa in Blacks of all ages (Schwartz, Schamroth, and Seftel, 1958; McLaren, 1969) but is almost always characterized by cardiac enlargement and congestive heart failure, neither of which was detected in the Soweto children. Subvalvar left ventricular aneurysms are a recognized entity in this community (Kanarek *et al.,* 1973) and, therefore, must be considered as a possible aetiological factor, but there was no other clinical or electrocardiographic evidence to suggest their presence. Though there were no overt features of Marfan's syndrome, it is possible that a similar pathological process affecting the mitral valve mechanism accounted for some of the non-ejection clicks or mitral systolic murmurs in these children. Such patients with no skeletal manifestations of Marfan's syndrome have been previously recognized and the condition has been referred to as the 'floppy valve syndrome' (Read, Thal, and Wendt, 1965). When this presents with significant mitral regurgitation at a young age or with associated aortic, pulmonary, or organic tricuspid regurgitation the 'floppy valve syndrome' is a likely diagnosis. However, in the early stages, a late systolic murmur or non-ejection click may be the only signs and it may be impossible (Barlow and Pocock, 1975) to differentiate this *forme fruste* of Marfan's syndrome from the 'billowing mitral leaflet syndrome'.

The two probable underlying aetiological factors for these auscultatory findings in Soweto children are either the specific entity of the 'billowing mitral leaflet syndrome' or rheumatic heart disease. In this same survey, an overall prevalence rate for rheumatic heart disease of 6·9 per 1000 was obtained in children aged 2 to 18 years, and a peak rate of 19·2 per 1000 in children of the seventh school grade was recorded (McLaren *et al.,* 1975). It is obviously important in the management of children with late systolic murmurs or non-ejection clicks to determine whether rheumatic heart disease is a factor in their pathogenesis. Though it was disputed by some workers (Tavel, Campbell, and Zimmer, 1965; Criley *et al.,* 1966; Jeresaty, 1973), there is now little doubt that rheumatic heart disease can give rise to these auscultatory findings (Leon *et al.,* 1966; Willems *et al.,* 1969; Epstein and Coulshed, 1973; Kalbian, 1973; Allen, Harris, and Leatham, 1974). Cobbs (1974) acknowledges that a late systolic murmur is not uncommon in rheumatic mitral regurgitation, but regards accompanying non-ejection clicks as being rare. However, in the Soweto survey, non-ejection clicks were audible in 3 children with established rheumatic heart disease, all of whom had an apical pansystolic murmur, and in 2 mitral stenosis was associated. Prolapse of the mitral leaflets has been shown by echocardiography in patients with rheumatic mitral regurgitation (Steinfeld *et al.,* 1974), and regression of the prolapse has been reported in some patients with disappearance of the systolic murmur. A decreased intensity or disappearance of the pansystolic murmur of rheumatic mitral regurgitation has been seen (Wilson, 1962; Kalbian, 1973; Barlow and Pocock, 1975) after the acute carditis has subsided, provided that recurrences of rheumatic fever are prevented. During this process of regression, the pansystolic murmur may become confined to late systole before disappearing (Pocock and Barlow, 1971; Cobbs, 1974). The mechanism for such reversible mitral regurgitation was assumed to be a consequence of healing of the inflammatory process involving the leaflets. Recently this concept has been challenged (Kalbian, 1973; Cobbs, 1974) and an alternative explanation that rheumatic coronary vasculitis results in temporary papillary muscle dysfunction has been postulated (Kalbian, 1973). In South Africa, pronounced dilatation of the mitral annulus is frequently seen in Black children with mitral regurgitation caused by rheumatic heart disease (Chesler *et al.,* 1966; du Plessis and Chesler, 1969), and the leaflets themselves may often be spared or only midly involved. Such annular dilatation may be the result of direct involvement of the annulus by the rheumatic process. In the early stages or where the process is mild, the physiological decrease in size of the annulus during ventricular systole may be partly or entirely lost and this feature could well be reversible (Barlow and Pocock, 1975). Temporary 'annular dysfunction' may thus play an important role in transient or partially reversible mitral regurgitation and explain the late systolic murmur observed in some patients. Alternatively, in those patients in whom the late systolic murmur persists, damage to the papillary muscle as a consequence of the rheumatic process may be a factor. A non-ejection click in patients with rheumatic heart disease may result from rheumatic involvement of the chordae tendineae, unequal prolapse of the mitral leaflets, or papillary muscle dysfunction.

Although the Soweto survey does not provide any conclusive evidence for a rheumatic aetiology of these auscultatory findings, it is relevant that there are also no factors that contradict this hypothesis. The epidemiology of rheumatic heart disease and these features was strikingly similar, but this may be largely non-specific and coincidental. Rheumatic heart disease was also more common in women (McLaren *et al.*, 1975) but a female preponderance has been reported in the billowing mitral leaflet syndrome (Pocock and Barlow, 1971; Jeresaty, 1973). The prevalence of both rheumatic heart disease and these auscultatory findings showed a strong linear relation with age and though this trend suggests that there is a constant exposure of these children to processes which then often leave a permanent residual lesion, it does not necessarily indicate that the operative aetiological agent is the same in both conditions. Rheumatic heart disease was also more prevalent in the higher primary schools (Fig. 2), and it is interesting that the prevalence rate was approximately equal to that of the late systolic murmurs and non-ejection clicks in the seventh school grade. Unlike these auscultatory findings, the prevalence of rheumatic heart disease dropped in the eighth school grade to 9·9 per 1000 which made us speculate (McLaren *et al.*, 1975) that this may be the result of a fall in attendance of older children who have more severe rheumatic heart disease or to a failure of such children to attain the higher school grade. Alternatively, the high prevalence in children of the seventh grade could be the result of a streptococcal epidemic in previous years. Undernutrition as a rough clinical assessment was more common in children with these features than in those with normal hearts, and if this is confirmed by anthropometric analysis it may indicate a higher susceptibility to the development of rheumatic fever. However, the billowing mitral leaflet syndrome is said to occur more commonly in asthenic individuals (Bon Tempo *et al.*, 1975). An important difference in the epidemiology of rheumatic heart disease and these auscultatory features was that the latter showed no correlation with family size and thus, by inference, with the degree of overcrowding, which has been shown (Gordis, Lilienfeld, and Rodriguez, 1969) to be the most significant factor in the epidemiology of rheumatic heart disease. The fact that the electrocardiograms of 11 children with non-ejection clicks or late systolic murmurs showed abnormalities described in the specific billowing mitral leaflet syndrome suggests that some of the Soweto children have this syndrome. However, the presence of a normal electrocardiogram in the remaining 147 children does not exclude the possibility of the billowing mitral leaflet syndrome and the aetiology still must remain in doubt. It is noteworthy that some workers (Steinfeld *et al.*, 1974; Barlow and Pocock, 1975) have not observed an abnormal electrocardiogram, such as is seen in the billowing mitral leaflet syndrome, in patients with a non-ejection click or late systolic murmur resulting from rheumatic heart disease.

Against the background of low socioeconomic status in Soweto and the high prevalence of rheumatic heart disease, it is possible that an unknown and probably large number of children with late systolic murmurs or non-ejection systolic clicks have mild rheumatic heart disease. Further elucidation of the problem is necessary. The only practicable method would be to follow up such children who are not on specific prophylaxis against rheumatic fever to observe the natural history and, where possible, to examine the members of their families to detect rheumatic heart disease or a familial incidence of the billowing mitral leaflet syndrome. Studies of the prevalence of these features in other population groups in which rheumatic heart disease is less prevalent would be contributory.

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# Arrhythmias in two patients with left ventricular bypass transplants[1]

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*Two patients who underwent left ventricular bypass transplants are described. Both patients sustained postoperative rhythm disturbances of their own hearts during sinus rhythm of the donor hearts. Illustrative examples of atrial flutter, ventricular flutter, ventricular fibrillation, blocked atrial extrasystoles, and double ventricular parasystole in the recipient hearts are presented. The patients tolerated all these arrhythmias well during uninterrupted sinus rhythm in the donor heart. The problems in interpretation of arrhythmias in the presence of two hearts are discussed.*

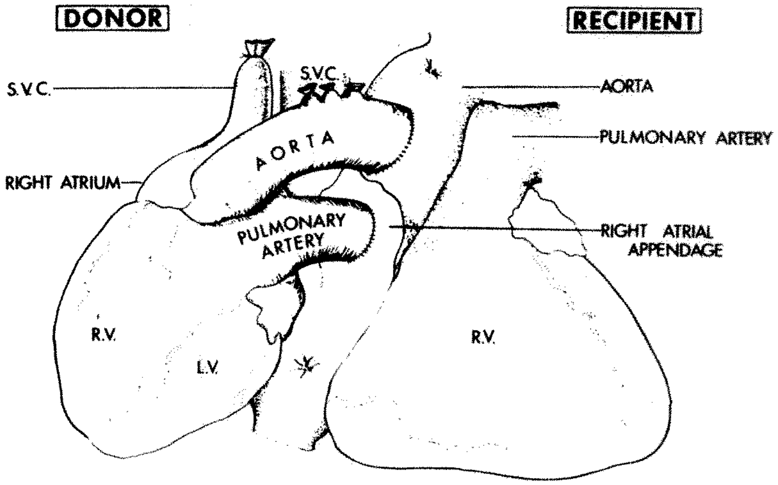

FIG. 1 *Position of donor and recipient hearts in anteroposterior view with relevant anastamoses (Barnard and Losman (1975). Reprinted with permission of* South African Medical Journal*).*

The purpose of this report is to illustrate some of the bizarre electrocardiograms resulting from cardiac transplantation in man where the recipient heart is left *in situ*. The surgical technique was described in detail by Barnard and Losman (1975). Briefly, the donor heart is implanted via a median sternotomy in the area anterior to the hilum of the right lung and in the right cardiophrenic angle. Both venae cavae of the donor heart are ligated and the donor right ventricle pumps only its coronary sinus venous return into the recipient's right atrium via the donor pulmonary artery (Fig. 1). The donor and recipient left atria are anastomosed side-to-side and the donor left ventricle is connected via ita aorta to the recipient aorta.

The sinus nodes of both hearts are intact, but that of the donor is denervated. Clearly, the

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rhythms of both hearts are totally independent and are subject to their own individual disturbances of rhythm. As will be shown, these are usually readily identified where one of the two hearts remains in sinus rhythm. The theoretical possibility exists, however, that the development of arrhythmias in both hearts simultaneously could give rise to considerable diagnostic difficulties.

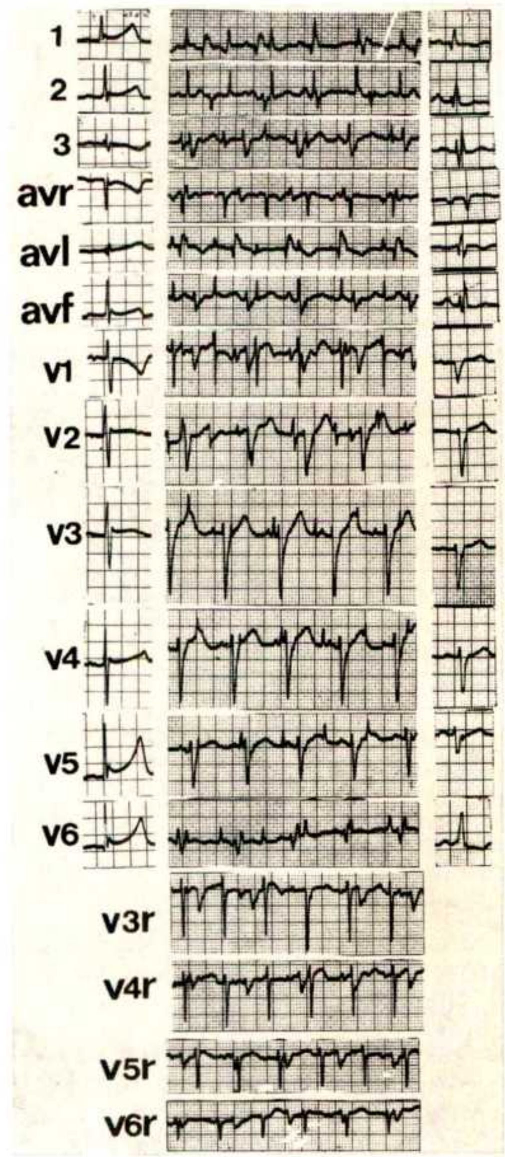

FIG. 2 *Case 1: Donor electrocardiogram on left, recipient electrocardiogram on right, and postoperative electrocardiogram showing both donor and recipient complexes in centre panel. Leads V1, V2, and V3 are half-standard on the recipient electrocardiogram.*

## Case reports

### Case 1

This 59-year-old man had a 10-year history of intractable ischaemic heart disease progressing to grade 4 effort intolerance. He had clinical evidence of biventricular failure, massive cardiomegaly, a third heart sound, and an electrocardiogram illustrated in the right-hand panel of Fig. 2 showing sinus rhythm with left atrial enlargement and left bundle-branch block. Chest *x*-ray film showed massive cardiomegaly with probable left ventricular aneurysm. Cardiac catheterization showed severe biventricular cardiac failure with significant pulmonary hypertension, and left ventricular angiography revealed extensive destruction of the left ventricular muscle with a chamber which was dilated and contracted very poorly; coronary angiography showed severe three-vessel disease.

In view of his severe symptoms and his unsuitability for a more conservative operation, transplantation of the type described above was recommended to circumvent the problem of his pulmonary hypertension which would otherwise have been a relative contraindication to conventional cardiac transplantation. At the time of operation there was diffuse fibrosis of the left ventricle of which about 20 per cent was excised; there was fresh clot in the left ventricular cavity. The donor heart was obtained from a 10-year-old girl who died of head injuries. Her electrocardiogram before death is illustrated in the left-hand panel of Fig. 2, showing sinus rhythm with pronounced J wave and prolongation of QT interval resulting from cerebral damage.

The centre panel of Fig. 2 illustrates the electrocardiogram obtained postoperatively showing both donor and recipient hearts in sinus rhythm. The recipient QRS complexes are readily identified by the presence of significant QRS widening as seen before operation. The frontal plane QRS axis of the donor heart is unchanged after transplantation. The frontal plane QRS axis of the patient's own heart has shifted from +75° before to −45° after operation. The horizontal plane QRS axis of the donor heart has undergone slight counter-clockwise rotation.

Fig. 3 illustrates the development of atrial flutter with 4:1 atrioventricular block on the 19th postoperative day at a time when the patient was fully digitalized. The flutter rate of the recipient heart is an exact multiple of the recipient ventricular rate and not of the donor ventricular rate, thus indicating that the atrial flutter originates in the recipient heart. This rhythm did not cause any haemodynamic disturbance and subsided spontaneously.

On the 22nd postoperative day the patient's condition deteriorated dramatically. He became dyspnoeic and restless with signs of poor peripheral perfusion and raised jugular venous pressure. Whereas previously both donor and recipient heart pulses had been palpable at the wrist, a single pulse wave only could now be palpated. Heart sounds were no longer audible over his own heart but could still be heard over the donor heart. Fig. 4 illustrates the electrocardiogram at this time. A regular ventricular rhythm of 138/minute is seen, with a QRS morphology of the donor heart. Ventricular fibrillation is clearly present in the recipient heart; this responded promptly to DC• countershock synchronized on the QRS complex of the donor heart.

Fig. 5 illustrates the development of ventricular flutter four months after operation in the same patient at a time when he had been readmitted to hospital for observation because of a respiratory infection. In many of the leads it is impossible to determine which heart is in ventricular flutter. However, with knowledge of the previous morphology of the QRS complexes of the two hearts in each lead, the donor heart complexes can be clearly identified in lead aVR at a rate of 170/minute,

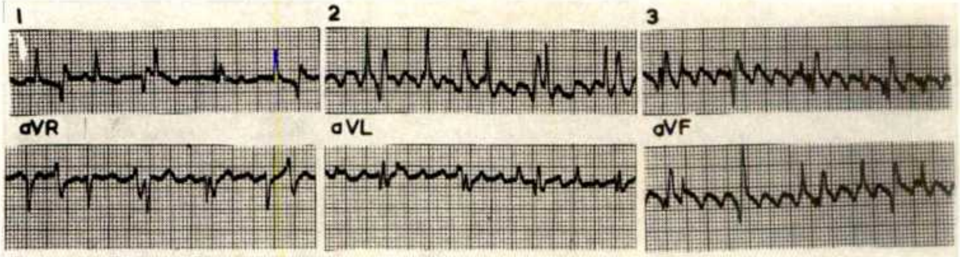

FIG. 3 *Atrial flutter with 4:1 AV block in recipient heart of Case 1.*

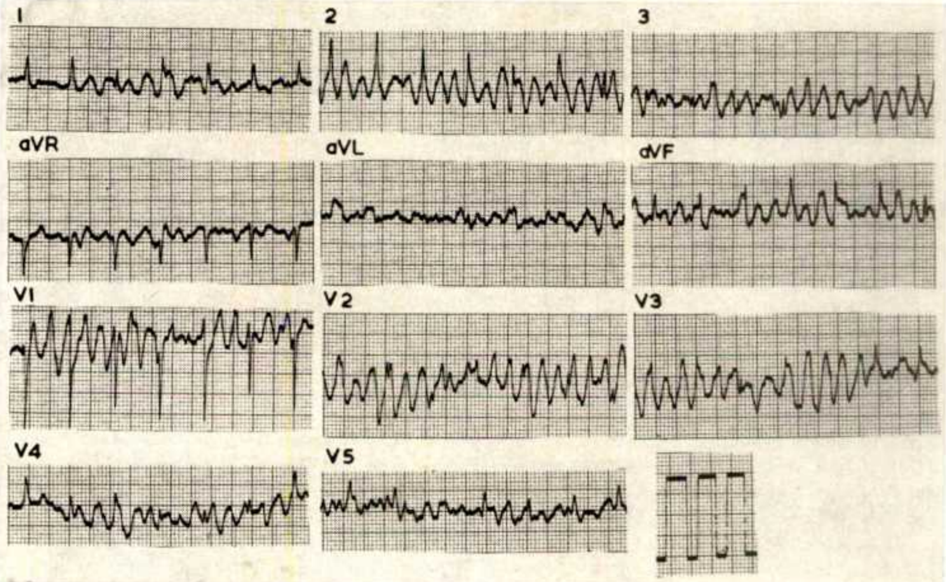

FIG. 4 *Ventricular fibrillation in recipient heart of Case 1.*

indicating that the recipient heart is the source of the arrhythmia. On this occasion his clinical condition was as it had been when he was in ventricular fibrillation previously. The arrhythmia responded readily to intravenous lignocaine.

Ventricular arrhythmias were prominent throughout his postoperative course and frequent multiform ventricular extrasystoles are readily seen in Fig. 6. The same record shows occasional 'dropped beats' in the recipient heart rhythm, the explanation of which is not obvious. The recipient RR interval is 600 ms. Though the negative P waves are less readily identified, they appear to precede each QRS by a fixed interval of 190 ms. During the gaps in recipient ventricular rhythm there is an interval of 960 ms without recipient QRS complexes. The RR intervals following two such gaps are 700 and 650 ms (Fig. 6). The likeliest explanation for this phenomenon, as illustrated in the accompanying ladder diagrams, is that the gaps are the result of atrial extrasystoles falling in the absolute refractory period of the atrioventricular conduction system and thus failing to conduct to the ventricles. These atrial extrasystoles reset the sinus node and depress its automaticity for the next few beats, thus accounting for the longer RR intervals and less obvious longer PP intervals which follow them. Because the P waves could not always be clearly identified, it is possible that the first QRS complex following each gap sometimes resulted

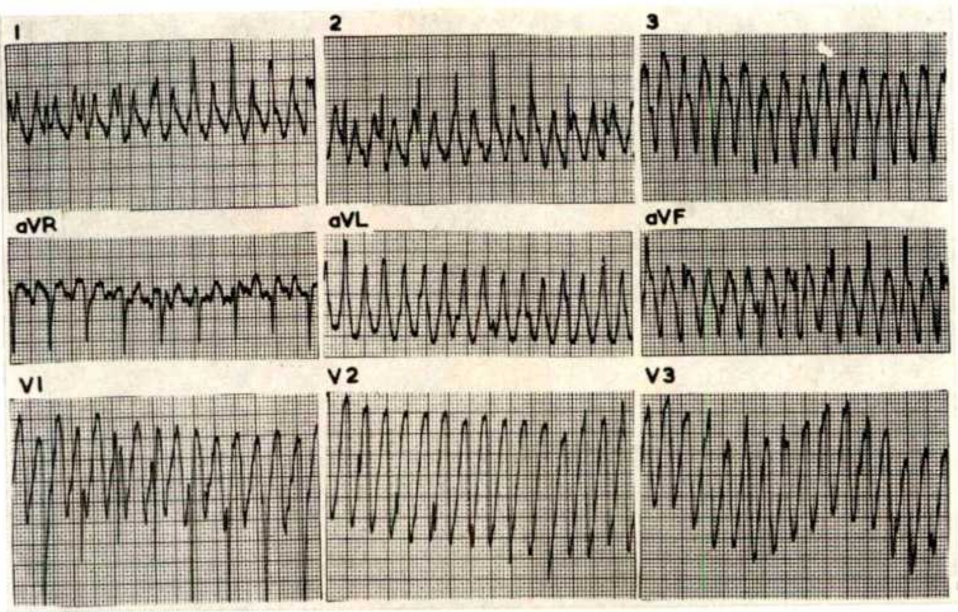

FIG. 5 *Ventricular flutter in recipient heart of Case 1.*

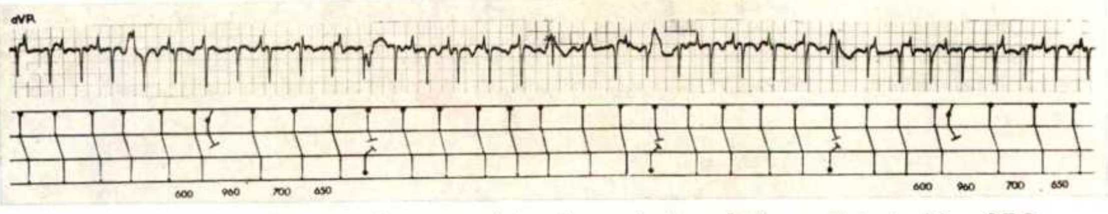

FIG. 6 *Ladder diagram relates to recipient heart rhythm which manifests positive QRS complexes. Three unifocal ventricular extrasystoles are seen. Two gaps in the recipient ventricular rhythm are caused by blocked atrial extrasystoles (Case 1).*

from a supraventricular escape focus with a different P wave morphology.

This patient's postoperative course was complicated by cerebral damage at the time of surgery from atheromatous embolism. This limited his mobility and he eventually died 132 days after transplantation from extensive pulmonary infarction as a result of emboli from bilateral femoral venous thromboses.

### Case 2

This 47-year-old man had an aortic valve replacement in 1969 for rheumatic aortic regurgitation with grade 3 effort intolerance. The aortic prothesis had to be replaced later the same year for fungal endocarditis unresponsive to medical therapy. Between 1969 and 1972 he was much improved symptomatically, but his condition then progressively deteriorated. On physical examination, he was in sinus rhythm with obvious cardiomegaly and trivial aortic regurgitation which had been present since his second aortic valve replacement. His electrocardiogram (right-hand panel of Fig. 7) shows that he was then in sinus rhythm with first degree atrioventricular block, left atrial enlargement, left axis deviation, and left bundle-branch block. Chest *x*-ray film showed generalized massive cardiomegaly, and cardiac catheterization confirmed the clinical impression of severe biventricular cardiac failure, pulmonary hypertension, and low cardiac output; there was mild aortic regurgitation on aortography, but the left ventricle was dilated and contracted poorly on left ventricular angiography.

The patient was operated upon using the same technique as in the first patient. The donor was a 17-year-old girl who died of severe head injuries; her normal electrocardiogram is shown in the left-hand panel of Fig. 7.

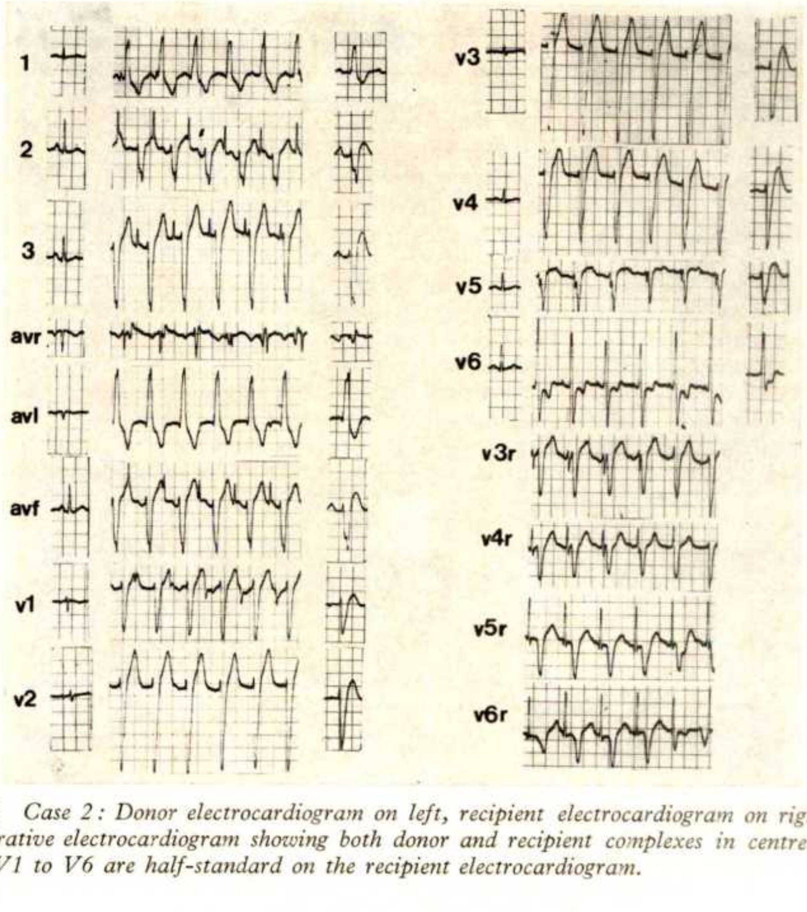

FIG. 7 *Case 2: Donor electrocardiogram on left, recipient electrocardiogram on right, and postoperative electrocardiogram showing both donor and recipient complexes in centre panel. Leads V1 to V6 are half-standard on the recipient electrocardiogram.*

The postoperative electrocardiogram of this patient is illustrated in the centre panel of Fig. 7 showing both donor and recipient hearts to be in sinus rhythm. In this case also, the recipient QRS complexes are readily identified by their significant widening which was present preoperatively. The frontal plane QRS axes of the donor and recipient hearts are unchanged. Leads V5R and V6R show qR complexes in the donor heart.

Fig. 8 shows a complex arrhythmia seen in this patient six weeks after operation. The small positive QRS complexes are those of the donor heart. Most of the wider negative QRS complexes are conducted beats in the recipient heart. QRS complexes of a different morphology marked with a cross (x) have a cycle length which is a multiple of 1220 to 1240 ms and interfere with the recipient QRS rhythm. Another type of QRS complex marked with a circle (o) which also interferes with the recipient QRS rhythm has a cycle length which is a multiple of 1420 to 1464 ms. Coupling intervals vary and these two ventricular rhythms are interpreted as being independent ventricular parasystolic rhythms with rates of 48 and 42 per minute, respectively, both originating in the recipient ventricle. Difficulties arise in the interpretation of the 16th recipient heart ventricular complex marked with an arrow; this has been interpreted as a sinus beat conducted with aberration. The 6th recipient heart ventricular complex is normally conducted, though the P wave follows the preceding recipient heart ventricular parasystolic complex (x) with shorter RP interval.

This patient has had recurrent attacks of ventricular tachycardia, presenting in the same way as in the previous patient, on four occasions since operation. One of these attacks occurred during cardiac catheterization a month after transplantation, while the others have occurred spontaneously and have responded on each occasion to intravenous lignocaine or cardioversion. His present treatment includes quinidine gluconate, propranolol, and digoxin, and has kept him free of these arrhythmias over the past two months, though Holter tape recordings have shown intermittent ventricular parasystolic rhythms similar to those illustrated in Fig. 8. The QRS morphology of the ventricular parasystolic rhythm has been unlike that of the ventricular tachycardias. At the time of writing, he is alive and well and back at work nine months after operation.

## Discussion

Changes in the electrical axis of both donor and recipient hearts in the frontal and horizontal planes are not unexpected in view of the inevitable distortion of the position of both hearts within the mediastinum. In patients with conventional heart transplants whose own hearts have been removed, postoperative rightward shifts in frontal axis are useful in diagnosing rejection (Griepp *et al.*, 1971). In the double heart transplant situation, however, the donor heart right ventricle is under considerably less haemodynamic stress as it pumps only its own coronary sinus venous return; it is, therefore, unlikely to dilate and this electrocardiographic sign will not be apparent with the development of rejection. Moreover, right ventricular biopsy as an index of rejection, as advocated by Caves and colleagues (1973), is impossible with the surgical isolation of the donor right atrium by ligation of the superior and inferior venae cavae.

It was of considerable interest to observe the effects of ventricular fibrillation on the haemodynamic status of the first patient. Not only was his donor heart alone able to maintain a sufficient cardiac output to maintain life, but the aortic pressure generated sustained coronary perfusion of his own heart sufficient to allow its defibrillation after several hours of ventricular fibrillation. Though the occurrence of further myocardial infarc-

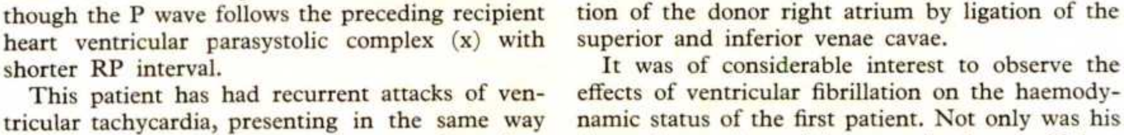

FIG. 8 *Ladder diagram refers to recipient rhythm which shows negative QRS complexes. Two ventricular parasystolic rhythms are shown; that marked with an (x) has a cycle length of 1220–1240 ms and that marked with an (o) has a cycle length of 1420-1464 ms. The 16th recipient ventricular complex marked with an (↑) is aberrant (Case 2).*

tion in his own heart to account for the development of ventricular fibrillation could not be substantiated electrocardiographically, raised serum levels of creatine phosphokinase isoenzymes suggested this possible diagnosis. The occurrence of ventricular tachycardia and/or fibrillation in the recipient hearts of both patients after operation precipitated right heart failure. This is a possible disadvantage of left ventricular bypass transplantation, which can be overcome by simultaneously bypassing both left and right ventricles: this has since been done in a further patient operated upon at this hospital.

The interpretation of electrocardiograms in the presence of two independent rhythms presents many difficulties. Comparison of the preoperative electrocardiograms of the donor and recipient hearts helps to clarify the origin of the QRS complexes. The fusion of P and T waves from both hearts, however, can give rise to difficulties in interpretation. Atrial and ventricular complexes should be chosen where the timing of donor and recipient rhythms are asynchronous to assist in interpretation. Fig. 6 illustrates the difficulty in defining the suspected presence of blocked atrial extrasystoles to account for the apparent gaps in the recipient ventricular rhythm. The intact autonomic control of the recipient heart can be used to help determine in which of the two hearts the rhythm disturbances are occurring, by the use of manoeuvres or drugs which influence autonomic control of the recipient heart rate but which would be ineffective in changing the rate and rhythm of the denervated donor heart.

Ventricular parasystole is commonly seen in patients with ischaemic heart disease. The electrocardiogram in Fig. 8 shows two independent ventricular parasystolic foci, with inherent discharge rates commonly seen in this condition. The 16th recipient ventricular complex in this electrocardiogram is interpreted as a sinus beat conducted with aberration, despite the fact that the 6th recipient ventricular complex with a shorter coupling interval after the preceding ventricular parasystolic complex is normally conducted. The suggested explanation is the presence of a gap in refractoriness of the right bundle-branch (Wellens, 1969) which results in a right bundle-branch type conduction pattern of the aberrant complex while an earlier sinus beat is normally conducted.

Interpretation of all the above electrocardiograms has been made easier by the fact that the donor heart remained in sinus rhythm throughout. Difficulties in interpretation are anticipated in the event of simultaneous rhythm disturbances in both donor and recipient hearts.

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# Motion of mitral apparatus in hypertrophic cardiomyopathy with obstruction

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*Motion of the mitral apparatus in hypertrophic cardiomyopathy with obstruction was investigated by conventional single dimensional and multidimensional echocardiography. In systole, anterosuperior displacement of the posterior papillary muscle, failure of mitral valve closure, and anterior motion of both mitral leaflets were shown. The anterior leaflet was seen to impinge on the posterior papillary muscle but not on the interventricular septum in systole. The abnormality of the single dimensional mitral echogram, previously ascribed to systolic anterior motion of the mitral anterior leaflet, was found to be a complex of echoes from the chordae tendineae, the papillary muscle, and, furthest from the septum, the mitral anterior leaflet.*

*It is concluded that systolic anterior motion of the mitral anterior leaflet is of smaller amplitude than others have suggested, and that obstruction to left ventricular outflow in hypertrophic cardiomyopathy is produced by systolic contact between the mitral anterior cusp and the posterior papillary muscle. The theory is put forward that displacement of the posterior papillary muscle above and in front of the mitral leaflets produces chordal slackening, and that it is displacement of the chordae tendineae by the blood flowing to the aortic root during left ventricular ejection, which is responsible for systolic anterior motion of the mitral leaflets.*

In patients who have hypertrophic cardiomyopathy with obstruction, systolic anterior movement of the mitral anterior cusp can be shown angiographically (Simon, 1968; Reis *et al.*, 1974). The workers who described the systolic abnormality of the single dimensional mitral echogram in this disorder, attributed it to abrupt systolic anterior motion of the mitral anterior leaflet (Shah, Gramiak, and Kramer, 1969; Pridie and Oakley, 1970), and so far their conclusions have not been challenged (Tajik and Giuliani, 1974; Rossen *et al.*, 1974; Bolton *et al.*, 1974; Henry *et al.*, 1975). Though possible mechanisms have been suggested (Shah *et al.*, 1969; Pridie and Oakley, 1970; Reis *et al.*, 1974; Henry *et al.*, 1975), the cause of the abnormal anterior movement has not been defined.

Single dimensional and multidimensional echocardiography (Roelandt *et al.*, 1974) were used to investigate motion of the mitral apparatus in hypertrophic cardiomyopathy. The findings are presented in this paper: in the light of them, the systolic abnormality of the conventional echocardiogram is reinterpreted and a new explanation of systolic anterior motion of the mitral leaflets is proposed.

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## Patients and methods

Four patients, three of them male, were studied: their ages ranged from 12 to 58 years. The clinical diagnosis of hypertrophic cardiomyopathy with obstruction had been confirmed by cardiac catheterization and all had a left ventricular outflow gradient at rest. Two were on treatment with beta-adrenergic blocking agents.

Single dimensional and, at a later date, multidimensional echocardiograms were recorded with the patients resting and semirecumbent. The single and the multiple element transducers were positioned to display maximal motion of the mitral anterior cusp and a long-axis view of the left ventricle, respectively.

The equipment for the single dimensional study was an Eskoline 20 ultrasonoscope (Smith Kline Instruments) interfaced with an ultraviolet strip chart recorder (Honeywell Visicorder). The multidimensional echocardiograms were recorded with a multiple element ultrasound system (Organon Teknika Echocardiovisor) which displays a moving two-dimensional echo image of the heart on an oscilloscope (Roelandt *et al.*, 1974). The dynamic

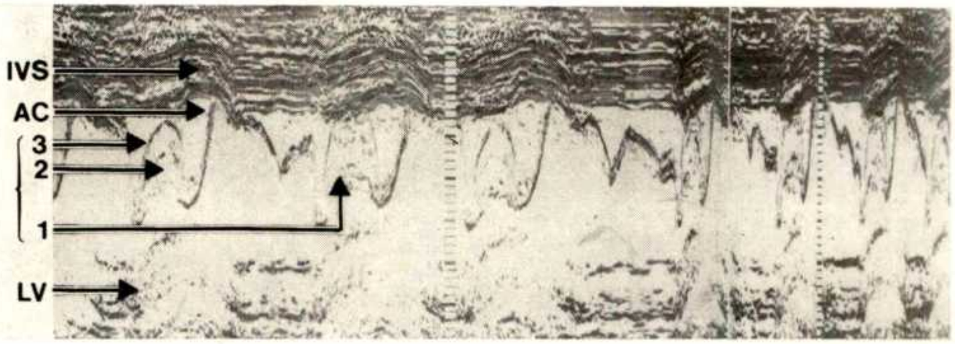

FIG. 1 *Single dimensional echocardiogram from a patient with hypertrophic cardiomyopathy with obstruction and atrial fibrillation. The echoes forming the systolic complex (see text) are numbered. In this and subsequent figures: AC = mitral anterior cusp, IVS = interventricular septum, LV = left ventricular posterior wall.*

display was stored on videotape using a slave oscilloscope and a television camera. Static Polaroid records were taken from the master oscilloscope with a camera triggered by the electrocardiogram (as in Fig. 3 and 5) and also from the videotape, using the stop-action facility on the video-replay system (as in Fig. 4 and 6).

## Results

### Single element scans

The mitral echogram comprised a single diastolic echo and multiple systolic echoes (Fig. 1).

**Diastole** A typical mitral anterior cusp echogram was recorded in diastole: the anterior cusp opened forwards impinging on the interventricular septum and closed at end-diastole to a point behind its end-systolic position.

**Systole** The echo complex recorded in systole had three components (Fig. 1, echoes 1, 2, and 3). First, a posterior echo (Fig. 1, echo 1), which was in continuity with the anterior cusp echo at end-diastole and end-systole and which moved anteriorly to a mid-systolic position well behind the interventricular septum. Second, a thin echo which moved rapidly forwards to and backwards from a mid-systolic position, close to or impinging on the interventricular septum (Fig. 1, echo 3): it was not recorded in early or end-systole and had no demonstrable continuity with the mitral anterior cusp echo. These two echoes thus formed the anterior (Fig. 1, echo 3) and posterior (Fig. 1, echo 1) edges of the systolic complex, the third component of which was a series of echoes (Fig. 1, echo 2) with characteristics similar to those of the myocardium of the left ventricular posterior wall (Fig. 1). They were recorded between the anterior and posterior echoes in mid-systole and were displayed as a narrow band in front of the posterior echo in early and late systole. Their continuity with the echoes of the left ventricular wall in the region of the posterior papillary muscle was apparent when the transducer was directed downwards (Fig. 2).

### Multiple element scans

Echo images of the aortic root, the anterior leaflet of the mitral valve, and the hypertrophied septum were recorded in both phases of the cardiac cycle; echoes from the posterior leaflet and from the posterior walls of the left atrium and left ventricle were less clearly defined (Fig. 3 to 6).

**Diastole** The mitral anterior leaflet moved rapidly forwards in diastole to a position where its free margin and an adjacent portion of the cusp impinged on the interventricular septum and where its tip lay in a vertical plane approximately mid-way between the anterior and posterior walls of the aortic root (Fig. 3). During this opening movement, the entire anterior cusp was orientated parallel with or convex to the interventricular septum (Fig. 4). At end-diastole, the anterior cusp moved rapidly backwards to a position where all of it, including the free margin, lay behind the vertical plane of the aortic root. The anterior and posterior mitral leaflets moved in opposite directions throughout diastole.

**Systole** Both mitral leaflets moved towards a closed position at end-diastole but the valve remained open. In early systole, though the anterior leaflet lay behind the vertical plane of the aortic

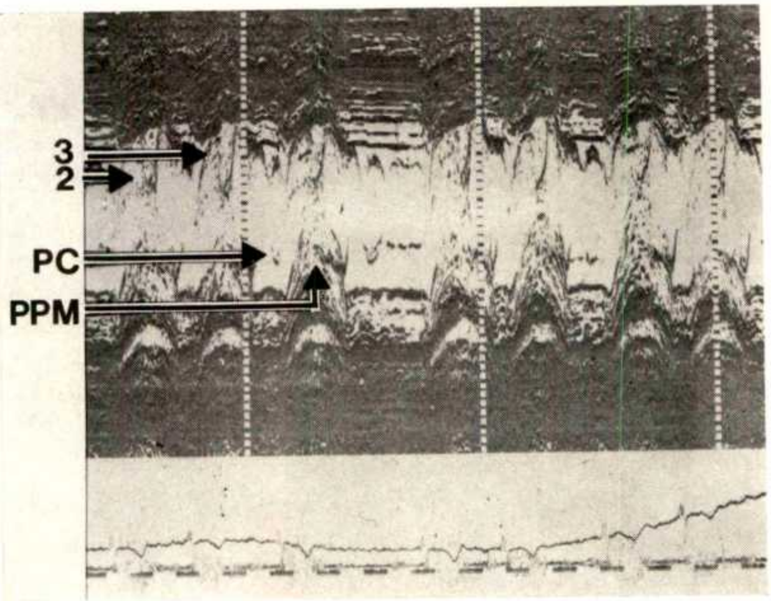

FIG. 2 *Single dimensional echocardiogram with simultaneous electro- and phonocardiograms from the same patient as Fig. 1. The ultrasonic beam has been directed downwards to the region of the posterior papillary muscle. The echoes forming the systolic complex (see text) are numbered: continuity between echo 2 and the papillary muscle echoes is apparent in the fourth cardiac cycle. In this and subsequent figures: PC = mitral posterior cusp, PPM = posterior papillary muscle*

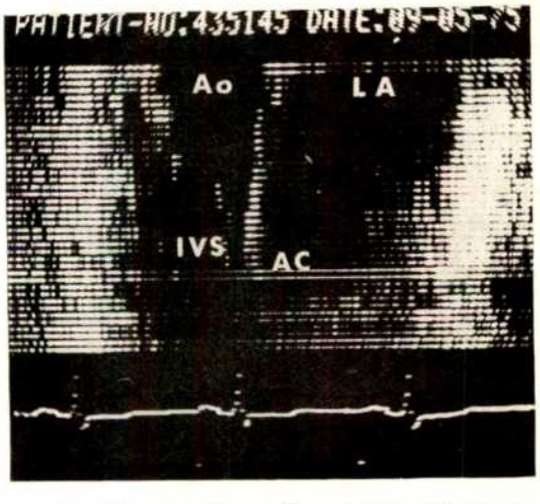

FIG. 3 *Hypertrophic cardiomyopathy with obstruction: multidimensional echocardiogram in mid-diastole. The tip of the mitral anterior leaflet impinges on the interventricular septum. In this and subsequent figures: Ao = aortic root, LA = left atrium.*

root and both leaflets presented a convex configuration towards the left atrium, their free margins were not in apposition (Fig. 5). Forward motion of both mitral cusps occurred in mid-systole: movement of the anterior cusp was maximal at, and close to, its free margin, and was slower and of smaller amplitude than the diastolic opening movement. Thus, while the remainder of the anterior leaflet maintained a more posterior position and a convex configuration towards the left atrium, its tip moved forwards into line with the posterior wall of the aorta and did not impinge on the septum (Fig. 6). At end-systole, the anterior cusp moved backwards for a short distance, but did not return to its more posterior end-diastolic position: details of posterior cusp motion were not defined.

Echoes which were not recorded in diastole intervened between the septal and anterior cusp echoes in systole (Fig. 5 and 6). The structure from which they originated moved upwards in the long axis of the ventricle in early systole to a position well above the tip of the anterior cusp. Its lower portion was closely related to the interventricular septum and, in mid-systole, to the tip of the mitral anterior

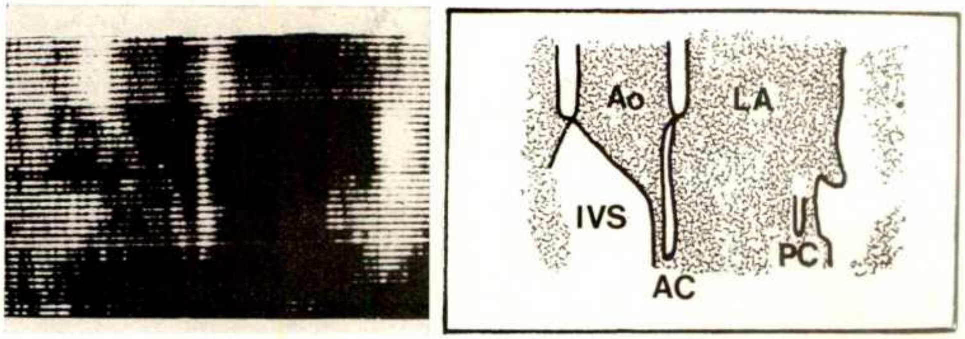

FIG. 4 *Multidimensional echocardiogram in late diastole from the same patient as Fig. 3 The mitral anterior leaflet is closely related to, but not in contact with, the hypertrophied septum.*

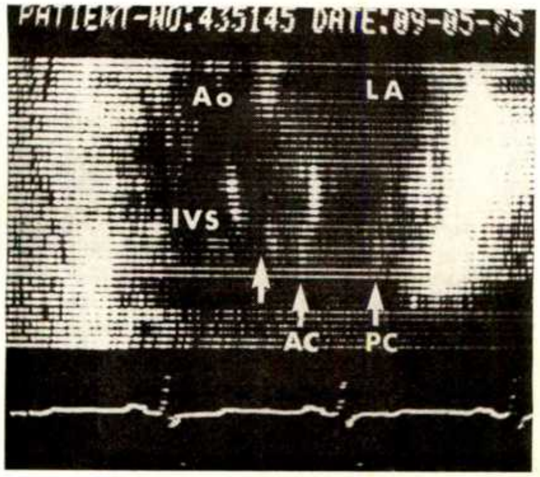

FIG. 5 *Multidimensional echocardiogram in early systole from the same patient as Fig. 3. The mitral leaflets are not in apposition. The structure (arrowed) which intervenes between the anterior leaflet and the septum has been identified (see text) as the posterior papillary muscle.*

leaflet (Fig. 6). Forward motion of the anterior leaflet appeared to be halted in mid-systole by contact with this structure.

## Discussion

The systolic abnormality of the conventional mitral echogram in hypertrophic cardiomyopathy with obstruction has been shown here to be an echo complex (Fig. 1). Previous workers (Shah *et al.*, 1969; Pridie and Oakley, 1970; Henry *et al.*, 1973) were thus wrong to ascribe it solely to systolic anterior motion of the mitral anterior leaflet. Its components have not been described before, though they can be seen in published tracings (Bolton *et al.*, 1974; Tajik and Giuliani, 1974; Henry *et al.*, 1975). For the reasons which follow, it has been concluded that they arise from the mitral anterior leaflet, the posterior papillary muscle, and the chordae tendineae (Fig. 1, echoes 1, 2, and 3, respectively).

Multiple element scanning has shown that the mitral anterior leaflet does not impinge on the inter-

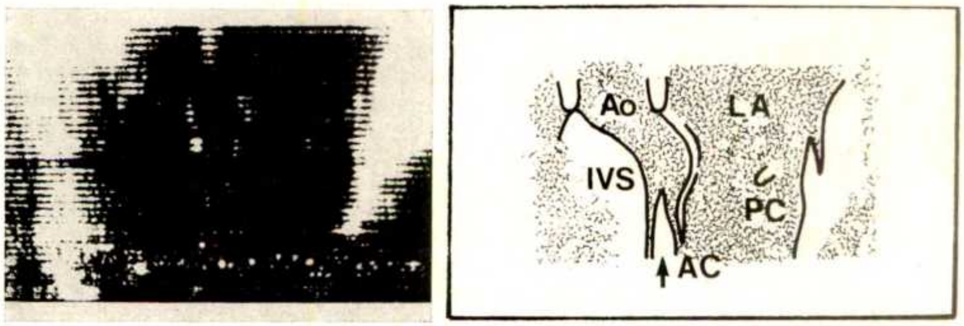

FIG. 6 *Multidimensional echocardiogram in mid-systole from the same patient as Fig. 3. The structure (arrowed) on which the anterior leaflet impinges has been identified (see text) as the posterior papillary muscle.*

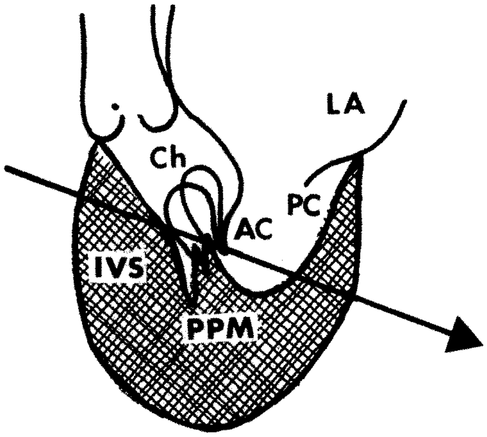

FIG. 7 *Hypertrophic cardiomyopathy with obstruction: a diagram of the left heart in mid-systole. Ch = chordae tendineae. It is suggested that the posterior papillary muscle and the chordae tendineae are displaced upwards and forwards. An ultrasonic beam (arrow) directed to the tip of the anterior leaflet thus passes in sequence through the interventricular septum, the chordae, the posterior papillary muscle, the mitral anterior leaflet, and the left ventricular posterior wall.*

ventricular septum in systole (Fig. 6) and that while systolic anterior movement of the leaflet does occur it is smaller and slower than its diastolic counterpart. Thus, the posterior element of the complex (Fig. 1, echo 1) is identified as the anterior leaflet echogram by its position, amplitude, and velocity as well as by its continuity with the anterior cusp echoes at end-diastole and end-systole. It follows that the two remaining elements of the complex arise from a structure or structures interposed between the septum and the anterior leaflet in systole. The only structures which could intervene in this position are the posterior papillary muscle and its chordae tendineae; echo images of all the other left heart structures accessible to ultrasound are recorded elsewhere on the systolic multiple element scans (Fig. 5 and 6). It has been concluded from their configuration that the echoes displayed in two dimensions between the anterior leaflet and the septum (Fig. 6) arise from the posterior papillary muscle: Henry *et al.* (1975) attributed similar though less anteriorly positioned echoes to papillary muscle, but did not specifically identify the posterior papillary muscle. Though it appears from the multidimensional records that the posterior papillary muscle is the sole structure interposed between the anterior leaflet and the septum, the single element scans suggest that the chordae also intervene. Thus, the differing characteristics of the two echoes recorded between the anterior leaflet and the septum in Fig. 1 are in keeping with their origins from two separate structures, only one of which (Fig. 1, echo 2) is muscular. It has, therefore, been deduced that echoes 2 and 3 of the systolic complex (Fig. 1) arise from the posterior papillary muscle and the chordae tendineae, respectively.

The interrelations of the echoes in Fig. 1 can be explained if, in systole, the septum and the components of the mitral apparatus are interrelated as suggested in Fig. 7. The failure to identify chordal echoes on the multidimensional records may well reflect the poor resolution of the multiple element ultrasound system. Henry *et al.* (1975), using a sector-scanner, achieved better echo definition: when their two-dimensional records are reviewed in the light of the present study, it is evident that the echoes which they have attributed to the tip of the anterior leaflet, could instead be from chordae displaced upwards and forwards into the left ventricular outflow tract, as in Fig. 7.

The findings of this investigation are not in total accord with the conclusions on mitral cusp motion drawn from angiographic (Simon, 1968; Reis *et al.*, 1974) and previous echocardiographic (Shah *et al.*, 1969; Pridie and Oakley, 1970; Henry *et al.*, 1975) studies. Thus, while systolic anterior motion of the anterior leaflet is confirmed, systolic contact between the leaflet and the interventricular septum is not (Fig. 5 and 6). Though the concept of left ventricular outflow obstruction by the anterior leaflet is upheld, contact between the tip of the leaflet and the posterior papillary muscle, rather than the septum, appears to be responsible (Fig. 6). The failure of leaflet apposition in early systole, shown here (Fig. 5), has been suspected angiographically (Simon, 1968): it follows that the valve does not reopen in systole, as has been suggested (Pridie and Oakley, 1970), and also that the mitral regurgitation of hypertrophic cardiomyopathy may be pansystolic. Anterior motion of the posterior cusp was seen in systole, but it is clear that, contrary to Simon's (1968) hypothesis, the posterior leaflet does not move with the anterior leaflet to obstruct left ventricular outflow (Fig. 6). Anterosuperior displacement of both papillary muscles has been shown angiographically (Reis *et al.*, 1974), but the close relation of the posterior papillary muscle to the interventricular septum and its displacement above the free margins of the mitral leaflets (Fig. 5 and 6) have not been emphasized before.

The cause of the systolic anterior movement of the mitral anterior cusp has been the subject of speculation (Simon, 1968; Shah *et al.*, 1969; Pridie and Oakley, 1970; Reis *et al.*, 1974; Henry *et al.,* 1975). The theory that it is the result of pull by abnormally directed papillary muscles has not been substantiated by this study. Thus, the posterior papillary muscle is displaced above and in front of the mitral leaflets (Fig. 5): from this position, because the apices of the two structures are not aligned, it is not mechanically feasible for the papillary muscle to exert traction on the leaflets. Further, if papillary muscle shortening, which was not shown, does occur in hypertrophic cardiomyopathy, posterior papillary muscle pull will be directed along the ventricular long axis and will tend to pull the leaflets downwards rather than forwards. Because it precedes it (Fig. 5), displacement of the papillary muscle has also been discounted as the direct cause of systolic anterior motion of the leaflets.

The theory is put forward that, in the setting of the diminished left ventricular transverse dimension (Henry *et al.,* 1975), anterosuperior displacement of the posterior papillary muscle produces chordal slackening, and that it is forwards and upwards displacement of the chordae by the blood flowing towards the aortic root during ventricular ejection that is responsible for systolic anterior motion of the leaflets. It is suggested that displacement of the chordae and anterior motion of the leaflets proceed until the anterior leaflet impinges on the posterior papillary muscle, producing left ventricular outflow obstruction. It is also postulated that failure of leaflet apposition in early systole is the result of papillary muscle displacement, with consequent loss of traction.

Posterior papillary muscle displacement is thus seen to be a fundamental abnormality which predisposes to systolic anterior motion of the leaflets and to left ventricular outflow obstruction, both of which can be regarded as functions of left ventricular ejection. It is of interest that, though their theories concerning mitral cusp motion are incompatible with the findings of this study, Henry *et al.* (1975) have concluded that hydrodynamic forces generated by left ventricular contraction are responsible for left ventricular outflow obstruction.

The lability of left ventricular outflow tract obstruction, its response to beta-adrenergic stimulation and blockade, and its disappearance as the systolic performance of the ventricle deteriorates (Goodwin and Oakley, 1972) are in keeping with the present hypothesis. Further support is lent to it by the fact that surgical relief of left ventricular outflow obstruction has been shown to depend on papillary muscle realignment (Reis *et al.,* 1974).

It has been concluded from this study that the echocardiographic obstruction index developed by Henry *et al.* (1973) measures not left ventricular outflow obstruction but chordal displacement: the inaccuracies which have been observed (Rossen *et al.,* 1974) are thus easily explained.

I wish to thank Dr. Robert Railton for his help with the technical aspects of the multidimensional study and Dr. Celia Oakley for her encouragement. The Echocardiovisor was supplied by the Scottish Home and Health Department for evaluation.

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# An echocardiographic study of the interventricular septum in constrictive pericarditis

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*Ten patients with constrictive pericarditis were studied echocardiographically with specific reference to interventricular septal dynamics. Abnormal movement of the interventricular septum was present in 8 patients and consisted of flattening in systole and unusual posterior motion in diastole. The aetiology of this type of movement is at present unknown but may be related to restriction of normal cardiac rotational dynamics. The interventricular septum also showed diminished degree of thickening (mean 21·2%). The amplitude of excursion was generally at the upper limit of or greater than normal. Left ventricular posterior wall amplitude of excursion was normal. Flattening of left ventricular posterior wall diastolic movement was seen in 4 patients. Right ventricular end-diastolic dimension was slightly increased (1·2 to 1·7 cm/m$^2$) in 5 of 8 patients with abnormal septal motion, but no haemodynamic evidence of diastolic volume overload was found. Posterior pericardial thickening was noted echocardiographically when posterior calcification was present. We conclude that the most common though non-specific feature of the echocardiogram in patients with constrictive pericarditis is abnormal septal motion. Flattening of left ventricular posterior wall diastolic movement, posterior pericardial thickening, and epicardial-pericardial separation may also occur.*

Echocardiography has been most useful in pericardial disease for the identification of pericardial effusion, but the value of this method in patients with constrictive pericarditis is not established with any certainty. It is believed that it may be possible to show a thickened pericardium, and that the posterior left ventricular wall may show flat motion during diastole (Feigenbaum, 1972). We report our echocardiographic findings in constrictive pericarditis to show that abnormal interventricular septal motion is an additional feature to be sought in this disorder.

## Subjects and methods

Ten patients, aged 20 to 68, were studied. All had undergone cardiac catheterization, and a diagnosis of constrictive pericarditis had been made on the basis of characteristic findings (Table 1). The aetiology of the disease was tuberculosis in 5, idiopathic in 4, and following *x*-ray therapy in 1. Pericardial thickening, usually generalized, was confirmed at operation in 8 patients. Pericardial stripping was sufficiently complete to expect a good functional result after operation. Operation was not performed in the remaining 2 patients but the clinical picture was sufficiently specific to reinforce the catheterization data.

Echocardiographic strip chart recordings were obtained by means of a Smith-Kline Instruments Company Ekoline 20A ultrasonoscope coupled to a Cambridge MC IV multichannel data system. A 7·5 cm internally focused 2·24 MHz transducer was used; the mitral valve and left ventricular cavity were located by scanning in the standard fashion employed by Feigenbaum *et al.* (1972). Interventricular septal and left ventricular posterior wall motion were recorded in the region of or below the level of the chordae tendineae. At this level, the mitral valve echo was either fragmented or not seen. Identification of endocardium or epicardium was based on appropriate damping manoeuvres. Simultaneous reference phonocardiograms, using Leatham suction microphones, were also recorded on the strip chart.

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TABLE 1 *Summary of cardiac catheterization data*

| *Case No.* | *Age/sex* | *Pressures (mmHg)* | | | | | *Cardiac index (l/min per m²)* |
|---|---|---|---|---|---|---|---|
| | | *Right atrium a/v (mean)* | *Right ventricle* | *Main pulmonary artery* | *PAW a/v mean* | *Left ventricle* | |
| 1* | 56 F | 16/16 (12) | 36/16 | 36/20 | 22/20 (16) | 120/20 | 2·0 |
| 2* | 20 F | 20/20 (18) | 36/20 | 36/20 | 24/32 | 110/22 | 2·5 |
| 3* | 65 M | 23/20 (17) | 39/16 | 39/17 | 17/20 (18) | 124/24 | 2·9 |
| 4† | 56 M | 30/25 (26) | 50/28 | 50/28 | 28/28 (24) | 140/28 | 2·7 |
| 5* | 40 M | 16/15 (14) | 29/15 | 29/15 | 20 (16) | 100/16 | 2·0 |
| 6* | 32 M | 22/14 (18) | 28/17 | 28/19 | 27/20 (18) | — | 2·0 |
| 7 | 58 M | 20/18 (18) | 44/17 | 44/17 | 25/22 (18) | 90/18 | 2·9 |
| 8 | 68 M | 20/20 (18) | 38/17 | 38/20 | 20/16 (18) | 130/20 | 2·0 |
| 9* | 53 M | 18/18 (16) | 26/16 | 26/16 | 23/14 (16) | — | 1·7 |
| 10* | 26 M | 18/15 (14) | 30/14 | 30/16 | 18/20 (14) | 110/16 | 2·0 |

*=operated; †=died after operation; a/v=peak a/peak v. PAW=Pulmonary artery wedge.
*Conversion from Traditional Units to SI Units:* 1 mmHg≈0·133 kPa.

The following measurements were made:

(1) Interventricular septal mimimum and maximum thickness, percentage change in thickness, and amplitude of excursion.

(2) Left ventricular posterior wall amplitude of excursion.

(3) Right ventricular dimension index using the method described by Diamond *et al.* (1971).

All measurements were made to the nearest mm, and were a mean of 5 readings. Pre- and post-operative tracings were obtained at comparable heart rates with no more than 10 beats per minute difference.

## Results

### Interventricular septum

The echocardiographic data are summarized in Table 2.

**(A) Septal motion** (1) *Systolic:* Normal septal movement as recorded may be briefly anterior after the onset of the QRS complex, but the main direction is posterior with a maximal displacement reached just before maximal anterior movement of the left ventricular posterior wall. Posterior septal movement did take place in 6 of 10 patients (Cases 1, 6, 7, 8, 9, and 10), but was diminished and atypical in 3 of these 6 (Cases 1, 6, and 8). In Cases

TABLE 2 *Summary of interventricular septal echocardiographic data*

| *Case No.* | *Age/Sex* | *Movement* | *Minimal thickness (mm)* | *Maximal thickness (mm)* | *% change* | *Amplitude of excursion (mm)* |
|---|---|---|---|---|---|---|
| 1 | 56 F | A (A) | 10 | 12 | 20 | 8 (8) |
| 2 | 20 F | A (A) | 8 | 10 | 25 | 8 (7) |
| 3 | 65 M | A (A) | 10 | 11 | 10 | 7 (6) |
| 4 | 56 M | A | 11 | 12 | 9 | 9 |
| 5 | 40 M | A (A) | 8 | 9 | 13 | 10 (7) |
| 6 | 32 M | A (A) | 10 | 12 | 20 | 8 (8) |
| 7 | 58 M | A | 7 | 9 | 29 | 8 |
| 8 | 68 M | A | 7 | 10 | 43 | 9 |
| 9 | 53 M | N (A) | 8 | 10 | 25 | 8 (7) |
| 10 | 26 M | N (N) | 11 | 13 | 18 | 6 (8) |
| No. | | | (10) | (10) | (10) | (10) |
| Range | | | 7–11 | 9–13 | 10–43 | 6–10 |
| Mean | | | 9·0 | 10·8 | 21·2 | 8·1 |
| 1 SD | | | 1·56 | 1·40 | 10·10 | 1·10 |
| 1 SE | | | 0·49 | 0·44 | 3·19 | 0·37 |

N=normal; A=abnormal; SD=standard deviation; SE=standard error.
Data obtained after operation are shown in brackets.

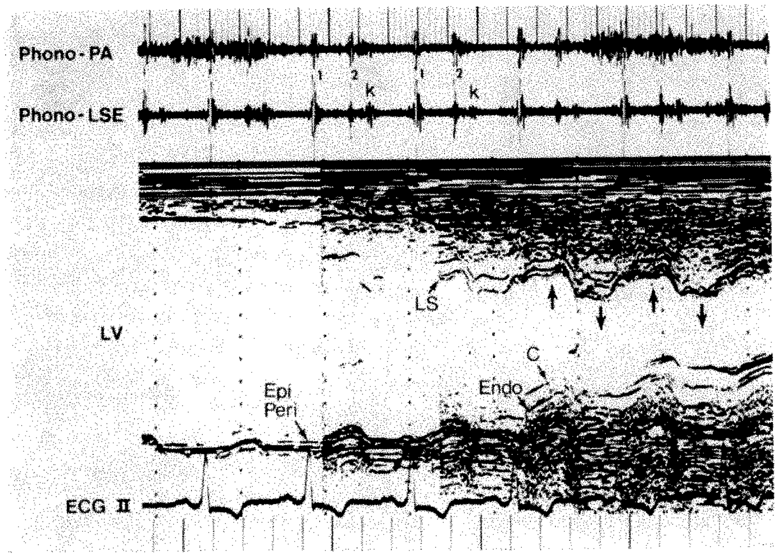

FIG. 1 *An example of abnormal interventricular septal motion from Case 4. Simultaneous phonocardiogram and lead II electrocardiogram. The vertical arrows emphasize the paradoxical motion of the septum. C=chordae. ENDO=endocardium. EPI=epicardium. LS=left side of the interventricular system. LV=left ventricular cavity. PERI=pericardium.*

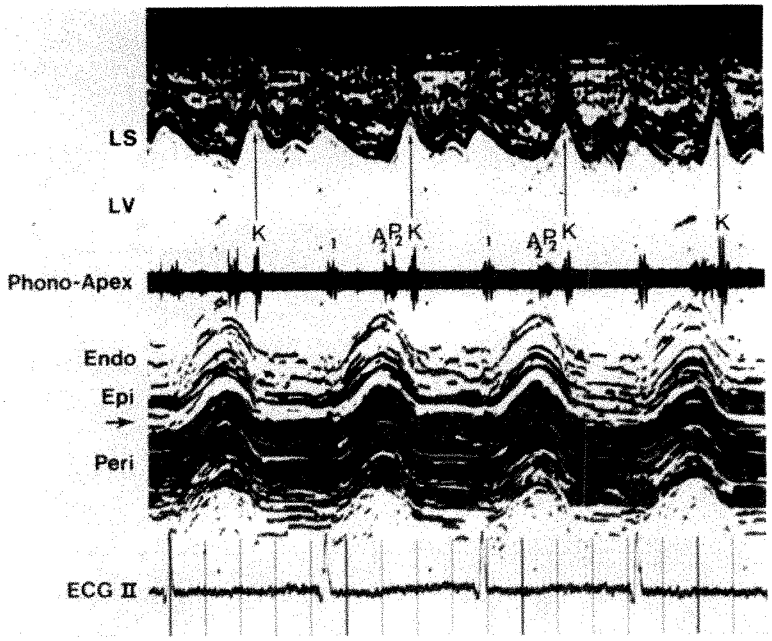

FIG. 2 *Left ventricular cavity in Case 7. A gap between the epicardium and pericardium is seen (horizontal arrow). A simultaneous apical phonocardiogram shows that the pericardial knock sound (K) coincides with a sharp reversal of interventricular septal movement (vertical arrows).*

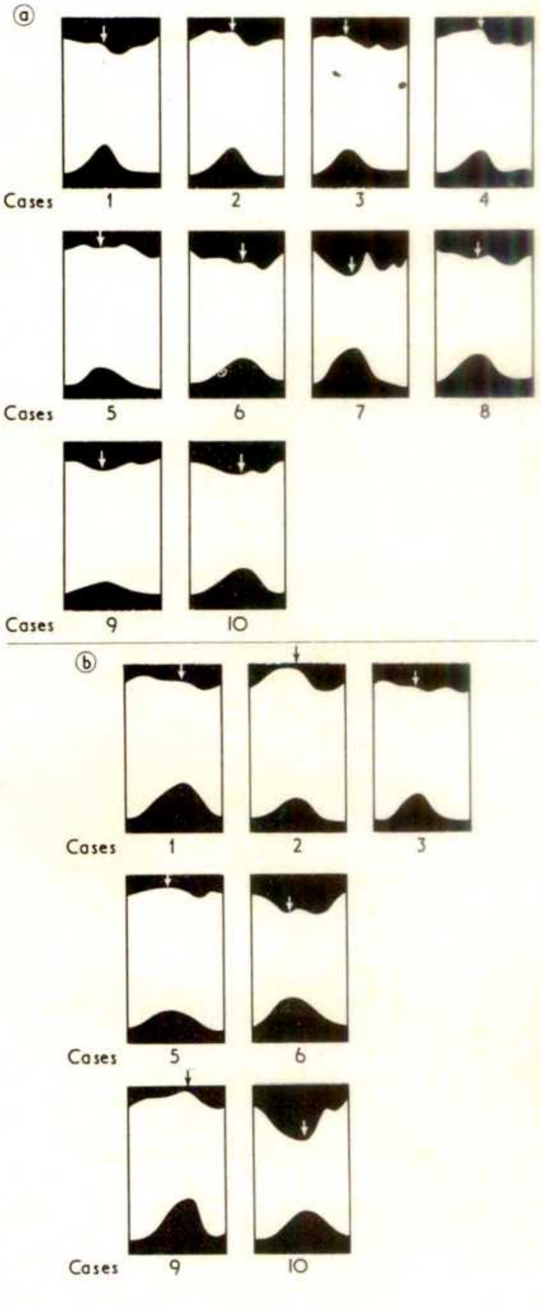

FIG. 3 *(a) Traced schematic representations of septal and left ventricular posterior wall movement in Cases 1 to 10. The onset and termination of the tracings are from peak to peak of the R wave of the electrocardiogram. The vertical arrow indicates the onset of the aortic component of the second sound. The amplitudes of wall motion are not directly comparable since the scales were different. (b) Traced, schematic representations of the postoperative data obtained in those cases that were studied.*

2, 3, 4, and 5, movement was anterior, biphasic, and flattened.

(2) *Diastolic:* After the second sound, three types of septal motion were seen. In group 1 (Cases 1–4), a major degree of posterior movement occurred immediately after the second sound (Fig. 1). In Group 2 (Cases 5–8), immediately after the second sound, there was either anterior or no motion followed by posterior motion at the end of rapid ventricular filling (Fig. 2). This type of posterior motion appeared as an exaggeration and persistence of the usually minor transient posterior motion seen in normal people at this time. In group 3 (Cases 9 and 10) the degree of movement was not sufficient to call definitely abnormal, but the expected asynchrony of maximal end-systolic septal and posterior wall movement was not apparent. In none of the 10 patients did the onset of posterior movement coincide with atrial systole.

**(B) Postoperative septal motion** It was possible to compare pre- and postoperative septal motion in 7 patients. The abnormal motion persisted in 5 and first appeared postoperatively in 1 (Case 9). In Case 10, posterior systolic movement of the septum was increased.

Fig. 3a and 3b show in diagrammatic form the movement of the left side of the interventricular septum and the left ventricular posterior wall pre- and postoperatively for the whole group of patients.

**(C) Septal thickness** Minimal septal thickness ranged from 7 to 11 mm, with a mean of 9·0 mm. These data are within the normal limits of our laboratory. Maximal septal thickness ranged from 9 to 13 mm, with a mean of 10·8 mm. This mean could indicate abnormal thinness since the normal range of our laboratory is 10 to 16 mm with a mean of 13·5 mm. However, only 2 patients fell outside the lower limit of normal. The mean percentage change in thickness of 21·2 per cent is reduced since our normal data range from 25 to 40 per cent, and 6 of the 10 patients are below normal.

**(D) Amplitude of excursion** The range for this measurement was 6 to 10 mm, with a mean of 8·1 mm. Our normal range is 3 to 8 mm so that 5 patients were at the uppermost limit of normal and 3 were in the hyperkinetic range.

## Left ventricular posterior wall

**(A) Left ventricular posterior wall movement** The pattern of left ventricular posterior wall endocardial diastolic movement was abnormally flat in 4 patients (Cases 1, 2, 3, and 4), and conformed to a previous observation by Feigenbaum (1972). One of these (Case 4) also showed slight late anterior motion in diastole. These observations are illustrated in Fig. 3A.

**(B) Left ventricular posterior wall amplitude of excursion** The range for this measurement was 9 to 11 mm, with a mean of 10·1 mm. This is within normal limits.

## Right ventricular dimension index

Mean right ventricular dimension index was 1·2 cm/m$^2$ (range 0·5 to 1·7). This mean is the upper limit of normal for our laboratory, and in 5 patients this index was above normal.

## Discussion

The principal echocardiographic feature of constrictive pericarditis in this study was abnormal interventricular septal motion. Anomalies of technique cannot be responsible for this since the observations were made at or below the level of the chordae tendineae. Hagan *et al.* (1974) have described the type of septal motion usually found in normal subjects at this level, which does not correspond in contour to that seen in 8 of the 10 patients studied. The character of the abnormal septal motion was variable though it most consistently resembled the B type described by Diamond *et al.* (1971). Thus, constrictive pericarditis must now be added to the growing list of disorders that are associated with this phenomenon.

The mechanism of this abnormal septal motion is obscure, and the established causes recently reviewed by Assad-Morell, Tajik, and Giuliani (1974) were not present. No electrocardiographic evidence of intraventricular conduction abnormalities, specifically left bundle-branch block, was noted. There was no evidence of cardiomyopathy or coronary artery disease. A right ventricular dimension index increase was found in 5 of 8 patients with abnormal septal motion but this was not of the degree usually seen in atrial septal defect or other conditions with right ventricular diastolic overload. Nevertheless the possibility of right ventricular diastolic overload could not be excluded. In order to study this further, simultaneous equisensitive right and left ventricular pressure records were obtained in one patient with normal septal motion (Case 10), who had the lowest right ventricular dimension index (0·5 cm/m$^2$) and in one patient (Case 3) with the highest right ventricular dimension index (1·7 cm/m$^2$). It was not possible in either patient to show interventricular pressure gradients in diastole. This suggests that the abnormal septal movement in constrictive pericarditis is not caused by right ventricular overload, since very small changes in right ventricular diastolic volume result in great increases in right ventricular diastolic pressure in this condition (Lewis and Gotsman, 1973). Respiration did not affect septal motion; since the degree of ventricular filling in constrictive pericarditis is not influenced by respiration, this is not surprising (Shabetai, Fowler, and Guntheroth, 1970).

At present any explanation of the abnormality found is hypothetical. The usual rotational character of ventricular movement with pivoting about the septum might be altered by fixation and relative immobility of the anterior cardiac surface. Adherence of the pericardium to the sternum or to the pleura was common at operation; this finding could explain a difference in the normal recording of the upper half of the interventricular septum with respect to the fixed position of the ultrasonic transducer. The range of abnormality of septal movement found may reflect the degree of adhesion, though the latter could not be quantified. A further relevant observation may be that we have not seen this type of abnormal septal motion in the only 3 patients with restrictive cardiomyopathy that we have studied by echocardiography. Apparent changes in interventricular septal thickness and movement might be the result of an unusual angle of incidence of the transducer beam. We propose to study septal mechanics by means of biventricular angiography, using the technique described by Redwood, Scherer, and Epstein (1974).

The persistence after operation of abnormal septal motion in our patients is most probably related to the type of incision used, since this echocardiographic finding has been noted in patients who have had median sternotomy for other cardiac disorders (Burggraf and Craige, 1975). This could also result from fixation of the anterior cardiac surface, though there are no experimental data on this point.

Left ventricular posterior wall diastolic movement was occasionally flat as has been reported by Feigenbaum (1972). This is primarily an epicardial and pericardial phenomenon though endocardial flattening was also seen. We would attribute this to decrease in ventricular compliance with little left ventricular filling occurring after the early diastolic rapid filling phase. This is not a finding confined to constrictive pericarditis since it has been seen in patients with other types of left ventricular pathology that diminish compliance.

Other epicardial and pericardial abnormalities have been seen in echocardiographic recordings. These include apparent thickening of the posterior pericardium, producing a single dense band of echoes (Feigenbaum, 1972). In addition two equally intense, parallel moving echoes, separated by a distance of 1 to 3 mm from the region of the posterior parietal surface of the visceral pericardium, were reported in patients with pericardial thickening (Horowitz *et al.*, 1974). Such findings were present in Case 7 who also had the most striking posterior calcification radiologically, and in Case 10 who also had posterior calcification. In our other patients, posterior thickening and a definite separation of the type described were technically difficult to define, and therefore not diagnostically helpful.

It is resonable to conclude, on the basis of the current findings, that the echocardiographic diagnosis of constrictive pericarditis will usually be by exclusion. Abnormal septal motion lacks specificity but may have high sensitivity. Flattening of the posterior left ventricular wall diastolic motion may be neither sufficiently specific nor sensitive. Obvious thickening of the posterior left ventricular wall lacks sensitivity but may be specific for calcific pericarditis. Nevertheless, a combination of echocardiographic findings, in conjunction with the clinical situation, may alert the physician to the possibility of this condition which may be difficult to diagnose.

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# Clinical experience with technetium-99m stannous polyphosphate for myocardial imaging

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*Myocardial imaging with technetium-99m stannous polyphosphate was performed on 46 patients. Eleven patients had no cardiac disease, 22 had acute myocardial infarction, and 13 had stable arteriosclerotic heart disease.*

*Distinct patterns of myocardial activity were noted: (1) the patients with no obvious cardiac disease showed no cardiac activity; (2) stable arteriosclerotic heart disease showed faint, ill-defined cardiac activity, primarily in the anterior or inferior aspect of the left ventricle; (3) acute myocardial infarction showed intense, focal, well-defined activity, with a shape that characterized the location of the infarct.*

Various centres are working to establish a method to estimate the size of a myocardial infarction. ST segment mapping (Maroko *et al.*, 1972) and determination of the isoenzymes of creatine phosphokinase (Sobel *et al.*, 1972) are two currently used investigative tools.

Recently, some workers have found that it is possible to use radioactive materials to detect the infarcted area (Gorten *et al.*, 1966; Hubner, 1970). Further a radio indicator sequestered by acute infarcted myocardium would also allow an estimation of the size of the infarction. Most of the techniques used in the past depended on failure of the ischaemic myocardium to take up the radionuclide, with a resultant negative image or a 'cold area'. Caesium-129 (Romhilt *et al.*, 1973), caesium-131 (Carr *et al.*, 1964), caesium-134 (Chandra *et al.*, 1973), rubidium-81 (Martin *et al.*, 1974), nitrogen-13 (Harper *et al.*, 1973), potassium-42 (Bennett *et al.*, 1972), potassium-43 (Zaret *et al.*, 1973), and radiolabelled fatty acids (Evans *et al.*, 1965), are radionuclides which provide this negative image. However, these materials cannot distinguish a recent from an old myocardial infarction and the physical and biological characteristics of these pharmaceuticals limit their clinical usefulness in detecting the infarcted tissue.

Bonte *et al.* (1974) have reported that technetium-99m stannous pyrophosphate can localize in the myocardium of dogs which have had experimentally produced myocardial infarction. Since the radionuclide accumulates in the necrotic area, it shows the lesion as an area of increased radioactivity, or as a hot spot.

In order to assess the clinical applicability of this new test, the following study was designed.

## Subjects and methods

Forty-six patients were studied, 11 of whom had no cardiac disease. The patients presented with chest pain and scintigrams were performed to rule out a myocardial infarction. Twenty-two patients had an acute myocardial infarction with typical history, electrocardiogram, and enzyme changes. Seven had subendocardial infarction and the remaining 15 a transmural infarction. The age of these 22 patients ranged from 47 to 86 (mean 60) years. Fourteen of the patients were men. Seven of the patients with an acute myocardial infarction had repeat scintigrams performed.

All 13 patients with stable arteriosclerotic heart disease presented with chest pain and had preexistent angina or an old myocardial infarction. A new myocardial infarction was subsequently not proven by serial electrocardiograms and enzyme studies. Their ages ranged from 36 to 87 (mean 63) years. Six patients were men.

Technetium-99m stannous polyphosphate, 15m

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Ci, was administered intravenously to each patient. The polyphosphate is manufactured by New England Nuclear Corporation. Two chains are present in this product. This isotope has a half-life of 6 hours which allows repetition of the study every 24 hours. In acutely ill patients the radioactive material was transported to the patient's bedside in an appropriate lead-lined safe, designed for carrying syringes. Sixty minutes later, left anterior and left lateral scintiphotos of the upper thorax were obtained. A high resolution colimator, 140 Kev, was centred at the point of maximal cardiac pulsation for both views. There were 300 000 counts per scintiphoto with a 20 per cent window. A Nuclear Chicago gamma camera was used to obtain the images. The images were recorded both on a Polaroid format and a 35 mm format. The 35 mm format is favoured since the areas of increased activity are more dramatically portrayed.

The patients suspected of having an acute myocardial infarction were accompanied to the Nuclear Medicine Laboratory with appropriate resuscitators, life support equipment, monitors, and in the presence of a trained intensive care unit nurse, medical resident, and intern. No patient was examined if the clinical condition was not considered stable by the cardiology group. The patient was not transferred from the stretcher for the examination, and it was not necessary to move the patient's body. The only necessary movement was to allow the patient's left arm to be extended above shoulder level while he lay supine. The arm was supported in this position for two minutes in order to obtain the left lateral scintiphoto. The total time necessary for the patient to remain in the Nuclear Medicine Laboratory for a complete examination, including positioning, recording, developing film, and provisional diagnosis, was approximately 12 minutes.

Fifty-three myocardial scans were obtained in the 46 subjects. Informed consent was obtained from all the patients.

## Results

Tables 1 to 3 tabulate the clinical information and the scan results on the 46 patients. No myocardial activity was found in the 11 patients without obvious heart disease (Fig. 1).

The patients with stable arteriosclerotic heart disease were studied 2 to 20 days after the onset of symptoms (mean 8·6 days). All but one of these patients had studies which showed faint, ill-defined activity, primarily in the anterior or inferior aspect of the left ventricle (Fig. 2). The acute myocardial infarction patients had images obtained 2 to 18 days after the onset of the infarct (mean 6·1 days). All these patients had intense, focal, well-defined increased activity in the region corresponding to the electrocardiographic localization of the infarction. A typical 'C' shaped zone of intense activity was seen in the anterior wall myocardial infarctions (Fig. 3) and a plate-like zone of increased activity was seen in the inferior wall myocardial infarction (Fig. 4).

Seven of the patients with an acute myocardial

TABLE 1 *Patients without arteriosclerotic heart disease*

| *Patient* | *Age* | *Sex* | *Chest pain* | *Discharge diagnosis* | *ECG* | *Highest* | | | *Scan* | *Scan days after admission* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *AST* | *CK* | *LDH* | | |
| FD | 69 | M | + | Carcinoma of prostate | Normal | 20 | 85 | 245 | No activity | 21 |
| RA | 41 | F | + | Carcinoma of tonsillar fossa | Normal | 15 | 50 | 280 | No activity | 4 |
| CC | 69 | M | + | Carcinoma of bladder | Normal | 20 | 60 | 100 | No activity | 5 |
| JM | 50 | M | + | Hypertension | Non-spec. ST-T wave changes | 20 | 35 | 240 | No activity | 4 |
| JD | 62 | M | + | Carcinoma of lung | Normal | 20 | 140 | 275 | No activity | 9 |
| CA | 42 | F | + | Metastatic carcinoma | Normal | 10 | 70 | 200 | No activity | 5 |
| EP | 63 | M | + | Rheumatic heart disease; mitral insuff. | Non-spec. ST-T wave changes | 20 | 35 | 245 | No activity | 5 |
| LP | 48 | M | + | Acute pericarditis | Non-spec. ST-T wave changes | 30 | 110 | 300 | No activity | 4 |
| CG | 53 | M | + | Carcinoma of lung | Normal | 9 | 65 | 255 | No activity | 5 |
| AR | 18 | M | + | Duodenal ulcer | Normal | 15 | 70 | 250 | No activity | 6 |
| AS | 65 | M | + | Syncope | Non-spec. ST-T wave changes | 23 | 220 | 245 | No activity | 5 |

Normal enzyme values=AST 7–40 units, LDH 150–400 units, CK 0–130 units.
*Note:* AST=aspartate aminotransferase; CK=creatine kinase; LDH=lactic dehydrogenase.

TABLE 2 *Patients with arteriosclerotic heart disease*

| *Patient* | *Age* | *Sex* | *Chest pain* | *Condition* | *ECG* | *Highest* | | *LDH* | *Scan* | *Scan days after admission* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *AST* | *CK* | | | |
| AG | 62 | M | + | Angina | Old anterior wall myocardial infarction | 30 | 55 | 305 | Faint activity | 14 |
| NS | 36 | M | + | Angina | Non-spec. ST-T wave changes | 15 | 75 | 220 | Faint ill defined activity | 3 |
| WS | 56 | M | + | Angina | Non-spec. ST-T wave changes | 22 | 55 | 250 | Faint activity | 3 |
| MC | 72 | F | + | — | Old inferior wall MI | 20 | 60 | 200 | Faint activity | 3 |
| BC | 87 | M | + | Angina | Non-spec. interventricular conduction defect | 33 | 60 | 185 | Faint activity | 3 |
| FW | 60 | M | + | — | Old anteroseptal | 23 | 115 | 390 | Faint activity | 5 |
| EL | 75 | F | + | Angina | Non-spec. ST-T wave changes | 34 | 60 | 350 | Faint activity | 14 |
| VW | 59 | F | + | — | Left bundle-branch block | 56 | 110 | 390 | Faint activity | 20 |
| CM | 71 | F | + | Angina | Right bundle-branch block | 40 | 140 | 295 | Faint activity | 9 |
| NL | 48 | M | + | — | Old anterior wall | 14 | 70 | 260 | Faint activity | 2 |
| HR | 58 | F | + | Angina | Non-spec. ST-T wave changes | 24 | 95 | 240 | Faint activity | 16 |
| MB | 81 | F | + | Congestive heart failure | Left ventricular hyper. | 27 | 165 | 290 | No activity | 15 |
| RF | 54 | F | + | — | Old anteroseptal MI | 24 | 65 | 340 | Faint activity | 5 |

For abbreviations, see Table 1.

TABLE 3 *Patients with acute myocardial infarction*

| *Patient* | *Age* | *Sex* | *ECG location* | *Highest* | | *LDH* | *Scan* | *Days after infarct* |
|---|---|---|---|---|---|---|---|---|
| | | | | *AST* | *CK* | | | |
| WN | 64 | M | Right bundle-branch block; anterior subendocardial MI | 66 | 635 | 315 | Focal increased activity—anterior | 9 |
| MJ | 43 | M | Anterior subendocardial MI | 50 | 300 | 445 | Focal increased activity—anterior | 7 |
| CV | 63 | F | Anterior wall MI | 225 | 1425 | 1000 | Focal increased activity—anterior | 2 |
| MM | 61 | F | Anterior subendocardial MI | 108 | 800 | 470 | Focal increased activity—anterior | 9 |
| MG | 62 | M | Inferior subendocardial MI | 62 | 435 | 410 | Focal increased activity—inferior | 3 |
| WD | 63 | M | Old inferior wall; new anterior subendocardial MI | 35 | 175 | 330 | Broad area activity, anterior and inferior | 7 |
| JL | 68 | M | Old inferior wall; new anteroseptal | 70 | 400 | 375 | Focal increased activity—anterior | 2 |
| CD | 86 | F | Anterior wall MI | 56 | 290 | 495 | Focal increased activity—anterior | 3 |
| US | 73 | M | Inferior wall MI | 60 | 340 | 425 | Focal increased activity—inferior | 3 |
| PT | 62 | M | Inferior wall MI | 286 | 2575 | 650 | Focal increased activity—inferior | 18 |
| RF | 63 | F | Anterior wall MI | 156 | 1470 | 950 | Focal increased activity—anterior | 9 |
| WJ | 47 | M | Anterolateral wall MI | 510 | 4700 | 1170 | Focal increased activity—anterior | 11 |
| GS | 48 | F | Anterolateral subendocardial MI | 33 | 270 | 335 | Focal increased activity—anterolateral | 5 |
| MG | 68 | F | Anterior wall MI | 45 | 480 | 395 | Focal increased activity—anterior | 10 |
| EV | 74 | F | Old inferior wall MI; new inferior wall MI | 60 | 200 | 400 | Focal increased activity—inferior | 4 |
| DN | 72 | M | Anterior wall MI | 50 | 180 | 425 | Focal increased activity—anterior | 3 |
| LS | 55 | M | Anterior wall MI | 37 | 305 | 320 | Focal increased activity—anterior | 6 |
| SD | 64 | M | Old inferior wall; new anterior wall MI | 198 | 1440 | 640 | Focal increased activity—anterior | 3 |
| HR | 69 | M | Inferior MI | 125 | 860 | 570 | Focal increased activity—inferior | 5 |
| JB | 56 | M | Anterior—subendocardial MI | 24 | 610 | 270 | Focal increased activity—anterior | 9 |
| CM | 62 | F | Anterior wall MI | 50 | 200 | 375 | Focal increased activity—anterior | 3 |
| LH | 60 | M | Inferior wall MI | 60 | 330 | 450 | Focal increased activity—inferior | 4 |

infarction (Table 4) had repeat scintigrams performed 14 to 32 days after the initial onset of symptoms (mean 22 days). Four of these follow-up studies showed less activity in the myocardium than the initial scintigrams. In these patients the enzymes had returned to normal values and the electrocardiogram had stabilized.

Three patients showed an increase in activity and a larger area of involvement. These patients also had clinical evidence of extension based on a new bout of chest pain, an increase in enzymes, and characteristic electrocardiographic abnormalities (Fig. 5 and 6).

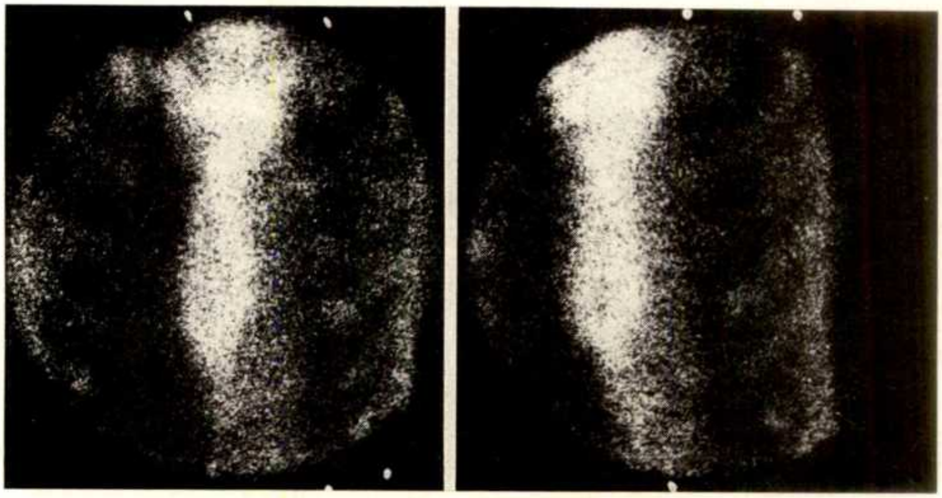

FIG. 1 *Anterior and left lateral scintiphotos of patient AR, with no cardiac disease. The ribs and sternum are well seen. There is no cardiac activity.*

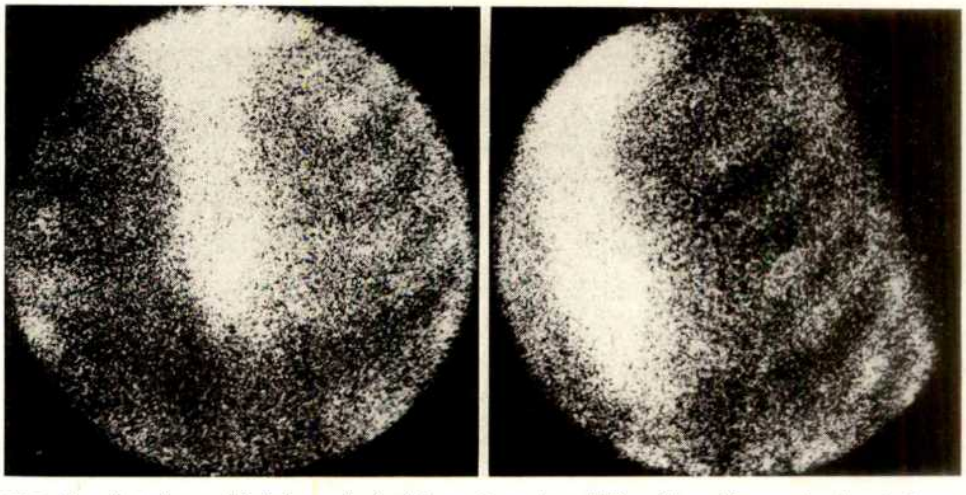

FIG. 2 *Anterior and left lateral scintiphotos in patient FW, with stable arteriosclerotic heart disease. Note the faint ill-defined activity.*

## Discussion

Bonte *et al.* (1974) determined that $^{99m}$Tc-stannous pyrophosphate can localize in the hearts of dogs with experimentally produced myocardial infarction. These authors suggested that with myocardial cell death there was a cellular influx of calcium ions which localized within the mitochondria in the crystalling structure hydroxyapatite. Since $^{99m}$Tc-stannous pyrophosphate labels hydroxyapatite for bone scanning, this isotope can also image fresh myocardial infarctions on the basis of the hydroxyapatite content. Other possible mechanisms include binding of phosphate to damaged cell membranes, uptake in other cytoplasmic or nuclear organelles, or binding to leucocytes invading the infarcted area.

Subsequently the same group performed myocardial scans on 15 patients with acute myocardial infarction (Parkey *et al.*, 1974). Thirteen patients had scans 3 to 7 days after the infarction and these were strongly positive in the regions corresponding to the electrocardiographic localization of the infarction. The remaining 2 patients were scanned more than 9 days after the infarction and their scans were negative. They also studied 2 patients with

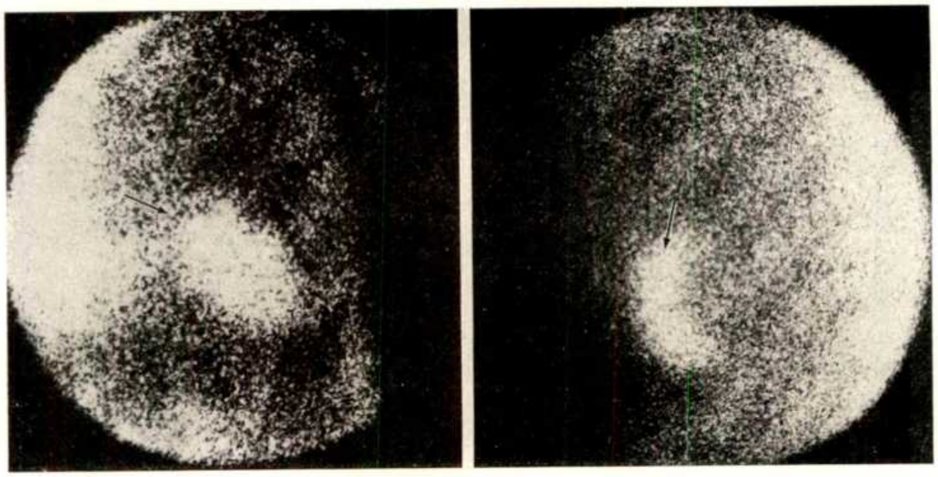

FIG. 3 *Anterior and left lateral scintiphotos in patient WN, with an acute anterior wall myocardial infarction. Note the 'C' shaped zone of intense activity in the lateral view.*

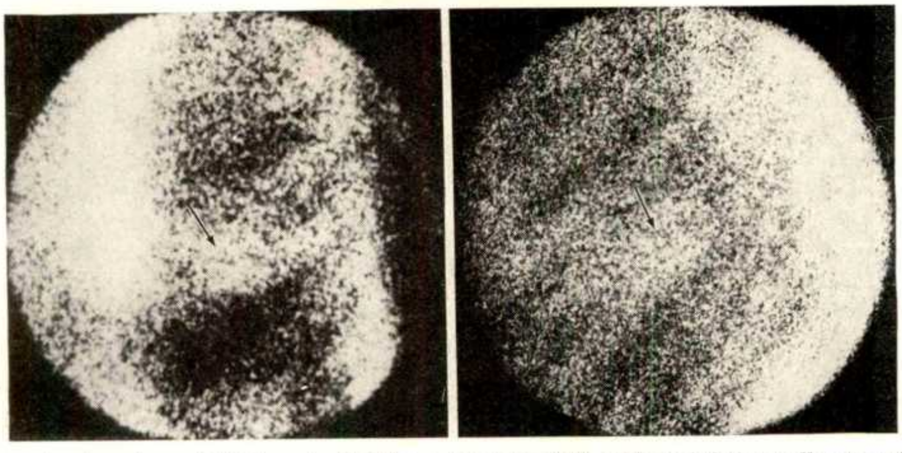

FIG. 4 *Anterior and left lateral scintiphotos in patient US, with an inferior wall myocardial infarction. Note the plate like zone of increased activity.*

stable arteriosclerotic heart disease and found questionable activity in their scintigrams.

Our present study supports and extends these observations. An acute myocardial infarction can be detected as early as 2 days and as late as 10 days after the infarction. Two patients in our study had positive scans 11 and 18 days after the onset of symptoms. However, they also had the highest CK values, which may explain the persistent activity. The myocardial activity is localized in the areas corresponding to the electrocardiographic abnormalities. Further, a characteristic 'C' shape zone of intensive activity was found in the anterior wall myocardial infarction while a plate-like zone of activity was found in the inferior wall myocardial infarction. Normal individuals show no cardiac activity. However, patients with stable arteriosclerotic heart disease do show faint ill-defined cardiac activity in the anterior or inferior aspect of the left ventricle. The exact reason that these scintigrams were faintly positive in these patients is uncertain, but several possibilities deserve mention. The positive scintigrams might indicate that there is a continual loss of small diffuse amounts of myocardial tissue caused by repeated bouts of myocardial ischaemia, or there may have been a

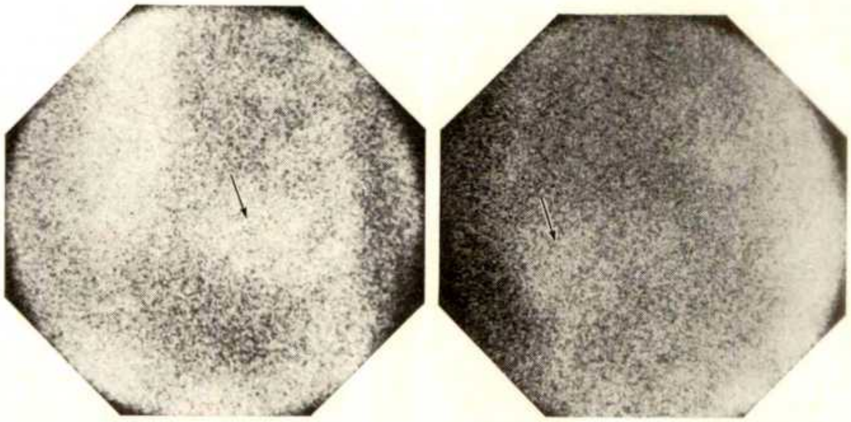

FIG. 5 *Anterior and left lateral scintiphotos in patient SD obtained 3 days after his anterior wall infarction. These photos are copies of the polaroids. Thus, the area of isotope uptake is white on a black background.*

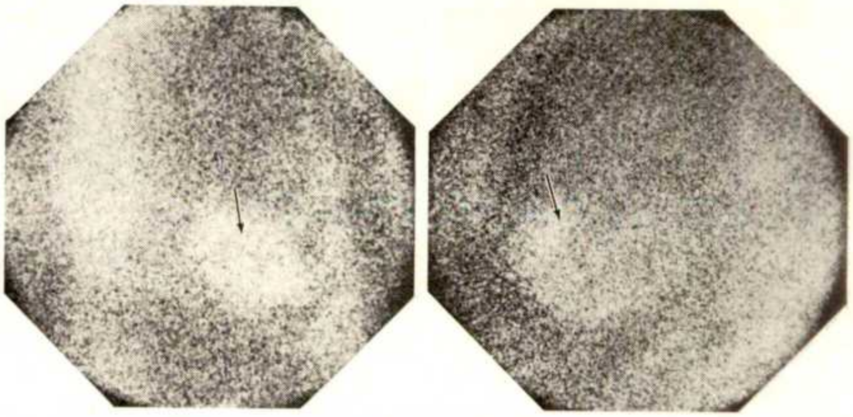

FIG. 6 *A repeat scintiphoto obtained 18 days after the infarction now shows a larger area of involvement.*

myocardial infarction in the distant past. However, it is very easy to separate the acute myocardial infarction with the focal intense activity from the minimal, non-focal cardiac activity seen in the stable arteriosclerotic patients.

Willerson *et al.* (1975) also administered technetium-99m stannous pyrophosphate to 17 patients with electrocardiographic and enzymatic evidence of an acute subendocardial myocardial infarction. In each patient the scintigrams were positive. However, it was not possible accurately to localize the area of myocardial damage in many of their patients. This is in contrast to the ability to localize fairly precisely the area of damage in transmural myocardial infarctions.

Botvinick *et al.* (1975) produced infarctions in 6 closed chest dogs. Scintiphotographs were taken 48 hours after the occlusion using technetium-99m pyrophosphate. Clear images of the infarction were obtained which correlated well with electrocardiographic localization. The animals were sacrificed and significant radioactivity was found only in regions of histologically confirmed infarction. Further the isotope localized specifically in areas of infarcted myocardium in amounts proportional to the degree of CK depletion. The authors concluded that these data provide strong support for the clinical application of this technique in the detection and quantification of acute myocardial infarction.

Willerson *et al.* (1975) have also subsequently reported in a larger series of patients that infarct size can be estimated from technetium-99m stannous pyrophosphate scintigrams. These authors are still not certain that some ischaemic but not necessarily irreversibly damaged cells may also label with technetium-99m pyrophosphate.

Bonte and his associates used technetium-99m stannous pyrophosphate for their studies. This agent is now limited to investigational use, while the $^{99\text{m}}$Tc-stannous polyphosphate is widely available. Both agents appear to give diagnostic scintigrams 60 minutes after the injection of the radionuclide. Further studies will be required to assess the relative merits of these two agents.

This new imaging technique can help to distinguish between an acute myocardial infarction and other conditions that cause chest pain. It may assist the surgeon by delineating precisely the area of damaged myocardium that may require operative intervention. It can detect an extension of the myocardial infarction. Most importantly, these tests can be carried out without danger or discomfort to the critically ill patient. Particularly if the institution is equipped with mobile scintillation cameras. The tracer is safe, inexpensive, and almost universally available.

Tetracycline labelled with $^{99\text{m}}$Tc can also detect a myocardial infarction as a 'hot' spot (Holman *et al.*, 1974). However, the optimal time for the scintiscan study using tetracycline labelled radionuclide is one to three days after the onset of chest pain. After three days little or no cardiac activity is observed. This contrasts with the $^{99\text{m}}$Tc polyphosphate studies. Positive scans can be obtained more than two weeks after the infarction. Further, the tetracycline labelled radionuclide produces a high uptake in the liver, resulting in difficulty in sizing diaphragmatic infarcts. Other radionuclides are currently being investigated. Technetium-99m

TABLE 4 *Myocardial infarction patients with follow-up scintigrams*

| *Patient* | *First scan* | *Days after infarction* | *Second scan* | *Days after infarction* | *Comment* |
|---|---|---|---|---|---|
| HR | Focal increased activity—inferior | 5 | Less activity—inferior | 14 | |
| LS | Focal increased activity—anterior | 6 | Less activity—anterior | 26 | |
| GS | Focal increased activity—anterolateral | 5 | No activity | 25 | |
| JM | Focal increased activity—anterior | 7 | Increased activity larger area | 14 | 8 days after infarction—chest pain, enzyme rise, anterior transmural MI |
| SD | Focal increased activity—anterior | 3 | Increased activity larger area—anterior | 18 | 15 days after infarction—chest pain, enzyme rise, T-wave inversion in praecordial lead |
| CV | Focal increased activity—anterior | 2 | More extensive involvement—anterior | 26 | 10 days after infarction—chest pain, enzyme rise, T-wave inversion in praecordial leads |
| MM | Focal increased activity—anterior | 9 | Minimal persistent activity | 32 | |

glucoheptonate has been found to be localized in areas of acutely infarcted myocardium in animals as well as in humans. Strauss *et al.* (1975) found that there was a good correlation between peak CK values and the percentage of the left ventricular area accumulating this isotope. Kramer *et al.* (1974) have reported that gallium-67 citrate can accumulate selectively in recently infarcted canine myocardium: the infarction appears as a hot zone. Gallium enters or is retained within the infarcted region as a result of the inflammatory cell response to the ischaemic cell damage.

Myocardial scanning appears to be a valuable technique for establishing the presence or absence of a myocardial infarction. These studies should be extended to gain more information about this new and promising test.

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# Anxiety after a heart attack

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*An objective measurement of anxiety at defined intervals after the onset of acute cardiac symptoms was made in 203 men admitted to the Coronary Care Unit, Royal Infirmary of Edinburgh, and in 83 patients in a Teesside coronary survey. Of the Teesside patients, 50 were treated at home, 22 were admitted initially to a coronary care unit, and 11 were admitted directly to a general medical ward.*

*In the Edinburgh patients the level of anxiety was high early in the illness, fell rapidly, and rose again towards the end of their stay in hospital. At 4 months it was that of a normal population. After transfer from the coronary care unit the group was not more anxious than other patients in the ward. Reaction to the illness was unrelated to its physical severity. Patients who reacted badly at the beginning were less likely to return to work.*

*The pattern of anxiety in the Teesside patients resembled that of the Edinburgh group, and reaction to illness was largely independent of physical aspects. Treatment in hospital, either through a coronary care unit initially or in a medical ward, did not increase emotional distress. At 3 months patients treated initially in a coronary care unit were less anxious than the others. Throughout the period of study the Teesside patients were more anxious than the Edinburgh patients and outcome was not related to anxiety. Social and environmental differences may account for this.*

An increasing number of patients with acute ischaemic heart disease are treated at the beginning of their illness in coronary care units. The physical benefits of continuous monitoring, early treatment of dangerous arrhythmias, and intensive care by highly trained staff have been discussed (Lawrie *et al.*, 1967), as have been the possible adverse psychological effects on the patient of such an environment and of subsequent transfer to open wards (Hackett, Cassem, and Wishnie, 1968; Dominian and Dobson, 1969). Rehabilitation may fail for psychological as well as physical reasons (Nagle, Gangola, and Picton-Robertson, 1971; Cay *et al.*, 1973), so it is important that treatment of the acute attack should not increase emotional disturbance.

This paper presents the results of two studies of anxiety in patients after a heart attack. The first group (group A) comprised 203 men admitted consecutively to the Coronary Care Unit of the Royal Infirmary, Edinburgh—a six-roomed purpose-built unit. Anxiety at defined intervals was measured and related to the physical diagnosis, severity of the attack, and outcome of treatment. At the same time an epidemiological survey of the incidence, mortality, and outcome in all cases of ischaemic heart disease in Teesside County Borough (now part of Cleveland County) was being carried out by a combined medical team. The opportunity was taken to measure anxiety in 83 consecutive cases (group B) by the same method and at much the same time intervals as in the Edinburgh study. Of the Teesside patients, 50 were treated at home by their general practitioner, 22 were admitted initially to a coronary care unit, and the remaining 11 were admitted directly to a general hospital ward.

The purpose of the study was to examine anxiety after a heart attack in the two very different populations and to relate this to the varying methods of treatment.

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## Method

Anxiety was tested by the Cattell 8-Parallel-Form Anxiety Battery (Scheier and Cattell, 1960). Each of the 8 forms of the battery consists of 7 brief, distinct subtests disguised in purpose and arranged

TABLE 1 *Measurement of anxiety in two groups*

| *Patient group* | *Time of testing* | | | | | | |
|---|---|---|---|---|---|---|---|
| Group A (Edinburgh) | Within 24 hours of transfer from coronary care unit to ward | 4th day | 7th day | 10th day | — | — | 4 months |
| Group B (Teesside) | Within 24 hours of notification of case to survey team | 4th day | — | — | 1 month | 3 months | — |

in a pencil and paper format. The battery facilitates repeated measurements of anxiety, with brief intervals between assessments, since all raw scores are transformed into standard scores with norms set at 5·5. The reliability of the forms has been tested and retested and found to be satisfactory (Philip, 1970) and British norms are available (Philip, 1972). Other considerations influenced the decision to measure anxiety by questionnaire and, in particular, by this test. It was thought inappropriate to use physiological indices of anxiety such as heart rate and blood pressure, which in these patients are likely to be related to physical state. The short, non-stressful nature of the test permitted testing to be carried out early in the illness and specialist personnel were not required to administer it. Table 1 details the time intervals of measurement in the two groups. These are not precisely the same because the time of testing had to be incorporated into the framework already in operation in the Teesside survey (Teesside Coronary Survey Report, personal communication).

The patients in group A were divided into those with definite myocardial infarction on the evidence of the electrocardiographic and biochemical tests, and those presumed to have myocardial ischaemia. The physical severity of the heart attack was calculated from coronary care unit data by means of the prognostic index described by Peel *et al.* (1962), which scores various factors in the previous history and clinical examination. The higher the total score the worse the patient's prognosis. The Teesside patients were classified as 'definite', 'possible', and 'not' cases of myocardial infarction by reference to a combination of historical, electrocardiographic, and biochemical criteria by 4 specially-trained nurses who also performed the tests of anxiety. It appeared that those classified as definite cases of myocardial infarction in the two groups were comparable and that the Edinburgh 'ischaemics' were equivalent to the Teesside 'possibles'.

## Results

### General characteristics of study groups

The ages of the 203 Edinburgh patients ranged from 16 to 79 years, with a mean of 55 years. Myocardial infarct was confirmed in 131 (65%), 101 (50%) being seen after their first major attack. Of those without myocardial infarction (the ischaemic group) 45 (22%) had no history of a previous myocardial infarction and 27 (13%) had such a history. On average, the infarct patients stayed 20 days in hospital and the ischaemic patients 12 days. Twelve patients died in hospital after transfer from the coronary care unit and 11 died within four months of discharge.

Of the 83 Teesside patients, 41 (49%) were classified as having a definite myocardial infarct, 26 (32%) as being possible myocardial infarction while 16 (19%) did not have an infarct. The diagnosis in the different treatment groups and the ages of the patients are shown in Table 2. As might be expected, more patients admitted to hospital, especially those sent into the coronary care unit, had a definite myocardial infarct than those treated at home. Age did not appear to affect the decision whether to treat at home or send into hospital.

TABLE 2 *Physical diagnosis and age of 83 Teesside patients related to method of treatment*

| | *Method of treatment* | | |
|---|---|---|---|
| | *Treated at home* | *Treated in hospital ward* | *Treated initially in coronary care unit* |
| No. of patients | 50 | 11 | 22 |
| *Diagnosis* | | | |
| Definite MI | 15 (30%) | 8 (73%) | 18 (82%) |
| Possible MI | 19 (38%) | 3 (27%) | 4 (18%) |
| Not MI | 16 (32%) | — | |
| *Age (y)* | | | |
| Range | 29–69 | 30–68 | 37–67 |
| Mean | 53·4 | 56 0 | 52 4 |

TABLE 3 *Anxiety scores in 203 Edinburgh patients (Group A)*

| *Time of testing* | *Myocardial infarct patients (131)* | | *Ischaemic patients (72)* | | *Total group (203)* | |
|---|---|---|---|---|---|---|
| | *No. tested* | *Mean score* | *No. tested* | *Mean score* | *No. tested* | *Mean score* |
| Day 1 | 111 | 6·4 | 61 | 6 5 | 172 | 6·4 |
| Day 4 | 113 | 4·9 | 52 | 5·3 | 165 | 5·0 |
| Day 7 | 107 | 4·9 | 38 | 4·5 | 145 | 4·8 |
| Day 10 | 102 | 5·2 | 25 | 5·2 | 127 | 5·2 |
| Four months after discharge | 89 | 4·4 | 42 | 4·7 | 131 | 4·5 |

Mean scores for normals set at 5·5.

## Measurement of anxiety (group A)

On the day after their transfer from the coronary care unit 172 (85%) patients were judged physically fit to complete the questionnaire. Table 3 details the test scores during the first 10 days of convalescence in the ward. The decrease in the number who completed the later tests was largely because many of the ischaemic patients were discharged early. Of the 12 patients who died in the ward 10 had had a myocardial infarct on admission, and this also decreased the number tested. The patients' level of anxiety was high immediately after transfer from the coronary care unit and then fell quite rapidly over the next week, rising again as discharge from hospital became nearer. Not surprisingly, immediately after their heart attacks they were more anxious than normal but they quickly settled in the ward, approaching normal anxiety levels again towards the end of their hospital stay. They were not, however, significantly more anxious than their fellow patients in the ward; the mean scores of those admitted directly to the ward as medical emergencies was 5·8.

The close similarity between the myocardial infarct and ischaemic patients in their level of anxiety suggests that the individual's reaction to his heart attack bears little relation to its physical severity. This was confirmed by the calculation of the correlations between the anxiety scores and the Peel Index (Table 4)

TABLE 4 *Correlation between level of anxiety and physical severity of heart attack (group A)*

| *Physical severity* | *Anxiety* Day 1 | *Day 4* | *Day 7* | *Day 10* | *Four months after discharge* |
|---|---|---|---|---|---|
| Peel index | r=−0 02<br>NS | r=−0·01<br>NS | r=0·03<br>NS | r=0·08<br>NS | r=−0 2<br>P<0 01 |

Four months later the 180 survivors were recalled to a follow-up clinic: 166 (92%) attended and 131 completed anxiety questionnaires. The patients were less anxious (Table 3) than they had been in the ward and the group on the whole had lower scores than normal. Interestingly enough, when anxiety was correlated with the physical severity of their heart attack four months previously anxiety was higher in those who had been less physically ill (Table 4).

On admission to the coronary care unit, 154 (76%) patients were working, 14 (7%) were unemployed, and 30 (15%) had already retired. Four months after discharge 94 patients (69% of those working on admission) were back at work—85 of them in their previous jobs, though considerable adjustments to lighten the work load had been made in 33 cases. The activity at work of the 154 who were working on admission was graded to take into account such changes in employment and adjustments to previous jobs (Table 5) and related to the patient's level of anxiety just after transfer from the coronary care unit. Patients who had reacted badly at the beginning of their illness were less likely to be

TABLE 5 *Activity at work at 4 months related to anxiety immediately after transfer from coronary care unit (group A)*

| *Activity at work at four months* | *Anxiety score immediately after transfer from coronary care unit (mean score)* |
|---|---|
| Fully active in same or comparable job | 5·9 |
| Not fully active in same or comparable job | 6·7 |
| Less demanding job | 7 0 |
| Retired—not because of age | 7·0 |
| Net yet back at work | 6 5 |

TABLE 6 *Anxiety scores in 83 Teesside patients (group B)*

| *Time of testing* | *Patients in coronary care unit initially (22)* *Mean score* | *Patients admitted to hospital ward (11)* *Mean score* | *Patients treated at home (50)* *Mean score* |
|---|---|---|---|
| Day 1 | 6·9 | 7·4 | 6·9 |
| Day 4 | 6·3 | 6·3 | 6·2 |
| One month after onset | 6·8 | 6·9 | 6·4 |
| Three months after onset | 5·9 | 6·6 | 6·3 |

working within four months and, if working, to be back to their previous level of activity. When it is recalled that anxious patients had not necessarily had more severe heart attacks than the others it suggests that anxiety hinders successful rehabilitation.

## Measurement of anxiety (group B)

Table 6 shows the results in the Teesside patients. The pattern of anxiety after the heart attack was similar whether the patient was admitted to a coronary care unit, directly to the hospital ward, or treated at home—an initial high level falling during the first few days of illness, rising again at one month, and finally dropping once more three months after the onset of illness. There was no significant difference in anxiety at the beginning of their illness in the three different treatment groups. Only in those treated initially in the coronary care unit was anxiety lower at three months than on the third day of their illness. The single point at which the profiles showed a significant difference was when the drop in anxiety between 1 month and 3 months was compared; patients treated initially in the coronary care unit became less anxious over this time than those treated at home. An unexpected finding was that the Teesside patients, though they had much the same pattern of anxiety after their heart attacks, were more anxious than the Edinburgh patients at every test. Also their mean anxiety level was always above that of a normal population.

Fewer patients in the group treated at home had had a myocardial infarct compared with those admitted to hospital. Anxiety in the 34 patients with definite or possible myocardial infarcts who stayed at home was examined separately. On each occasion of testing the level of anxiety in the infarct patients was marginally higher than in those treated at home whose initial diagnosis was not confirmed (Table 7). If anything, patients with definite or possible myocardial infarcts at home appeared more anxious than those admitted to the coronary care unit, but the differences were not significant.

Anxiety was then correlated with a number of variables measured in the survey, such as personal details, past history, and clinical and biochemical assessments of the patient's physical state immediately after the beginning of his illness and one month later. There was no significant association between those variables and the patient's reaction to his illness apart from a weak relation between the serum hydroxybutyrate dehydrogenase enzyme level at the beginning of illness and the patient's initial anxiety score.

To try to find out why anxiety decreased in the group treated in a coronary care unit between one month and three months after their illness two factors were examined in these patients which might well have had a bearing on their level of anxiety—routine hospital follow-up and the extent of rehabilitation. There was no difference between the coronary care unit group and the ward group in their follow-up appointments, 75 per cent of both groups being seen routinely at the hospital. The mobility at one month of the patients diagnosed as having a definite or possible myocardial infarct is shown in Table 8. At this stage, though the mean anxiety scores in the three treatment groups were practically the same, their progress was very different, the coronary care unit patients being the least mobile.

The results of a questionnaire sent at 3 months to a random sample of 200 patients in the Teesside

TABLE 7 *Anxiety in patients with definite or possible myocardial infarction treated at home (group B)*

| | *Definite myocardial infarction* | *Possible myocardial infarction* |
|---|---|---|
| Day 1 | 7·0 | 6·3 |
| Day 4 | 6·4 | 5·8 |
| 1 month | 6·7 | 6·0 |
| 3 months | 6·5 | 6·2 |

TABLE 8 *Mobility at one month of Teesside patients with definite or possible myocardial infarction (group B)*

| *Mobility at 1 month* | *Patients treated at home (34)* | *Patients treated in hospital ward (11)* | *Patients treated initially in coronary care unit (22)* |
|---|---|---|---|
| In bed | 2 (6%) | — | — |
| Up but not ambulant | 11 (32%) | 2 (18%) | 14 (64%) |
| Ambulant but housebound | 11 (32%) | 9 (82%) | 8 (36%) |
| Ambulant, not housebound | 7 (21%) | — | — |
| Missing data | 3 (9%) | — | — |
| Mean anxiety score at one month | 6·7 | 6 6 | 6·8 |

survey showed that return to work was not related to the method of treatment of the acute attack, except that hospital-treated patients were more likely to return to work without any restrictions.

## Discussion

The results of the Edinburgh study suggested that the individual's reaction to a heart attack was not related to the physical diagnosis or to the severity of illness. However, successful outcome of treatment, in terms of the patient's ability to earn a living afterwards, was associated with the level of anxiety in the first few days after the attack. Patients who had reacted badly at this stage were likely to do less well. Thus the effect on morale of treatment in a coronary care unit was relevant to subsequent rehabilitation. Of the 203 patients, 83 per cent said they had been reassured by intensive care (Cay *et al.*, 1972). This together with their low level of anxiety within a few days of transfer from the unit and the finding that they were not more anxious than other patients in the ward suggested that admission to a coronary care unit had not upset them, but in the absence of a control group this remained only an inference.

The Teesside group presented an opportunity to examine patients treated in three different ways. Since the survey was concerned with examining current practice in the area there was no reason to suspect that the general practitioner's decision to admit his patient to hospital or not was affected by the survey. The evidence from the Teesside patients shows that admission to hospital, either to a coronary care unit or directly into a ward, does not further upset patients with a heart attack. Like the Edinburgh patients, their reaction to the illness was largely independent of its physical aspects. The place and kind of treatment does not play a significant role either, provided that the patient derives reassurance and encouragement from the setting.

The data from the present two studies do not explain the higher anxiety in the Teesside patients. There was no difference in the method of testing, and the discrepancies in the time of testing, which could not be overcome, could have played only a small part. It is interesting to speculate that the environmental differences between the two populations may be a factor. The Teesside patients were from a heavily industrialized area while many in the Edinburgh group were in sedentary occupations or employed in light industry, so that returning to work was feasible—indeed, nearly all returned to their previous employment.

In Edinburgh the outcome of treatment was related to anxiety. This was not found in the Teesside patients, where the differing amounts of mobility achieved by one month in those treated in the coronary care unit initially, in hospital, or at home were not reflected in differences in their level of anxiety. Though the coronary care unit patients were less anxious, return to work at three months was unrelated to the method of treatment of the acute attack. Again, the whole question of local social and environmental factors may have to be considered.

Taken together, the results of the two studies are clear. There is no evidence that admission to hospital and, in particular, to a coronary care unit increased emotional disturbance in these patients.

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# Intractable paroxysmal tachycardia caused by a concealed retrogradely conducting Kent bundle

## *Demonstration by epicardial mapping and cure of tachycardias by surgical interruption of the His bundle*[1]

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*Electrophysiological and epicardial mapping studies are described in a patient without pre-excitation who had intractable recurrent paroxysmal supraventricular tachycardia. Electrophysiological studies revealed fixed VA conduction times during both rapid ventricular pacing and coupled ventricular stimulation. Catheter mapping of atrial activation during retrograde conduction and during induced paroxysmal supraventricular tachycardia revealed early distal coronary sinus activation (posterior left atrium) relative to the low septal, low lateral, and high lateral right atrium. These studies suggested the presence of a concealed left-sided bypass tract.*

*The patient underwent surgical interruption of the His bundle for control of paroxysmal supraventricular tachycardia. Epicardial mapping of the atria (during ventricular pacing) confirmed the presence of a concealed left-sided bypass tract. Surgery produced antegrade AV block (while retrograde conduction was maintained) and total cure of paroxysmal supraventricular tachycardia. This is the first reported case of a concealed retrograde extranodal pathway documented by epicardial mapping.*

Recent studies in patients with re-entrant paroxysmal supraventricular tachycardia without apparent pre-excitation suggest that re-entry can either be within the AV node or involve the normal pathway and a concealed extranodal pathway (Denes *et al.*, 1973; Coumel and Attuel, 1974; Neuss, Schlepper, and Thormann, 1975; Spurrell, Krikler, and Sowton, 1974a, b; Zipes, DeJoseph, and Rothbaum, 1974). In the latter cases, the extranodal pathway is capable of only retrograde conduction and, therefore, concealed on the surface electrocardiogram. Differentiation between intra- and extranodal re-entry has both diagnostic and therapeutic implications.

In the present report, we describe the electrophysiological and epicardial mapping studies in a patient without ventricular pre-excitation who had recurrent, intractable supraventricular tachycardia, and who underwent surgical ablation of the His bundle. Preoperative electrophysiological studies suggested the presence of a left-sided concealed extranodal pathway capable of only retrograde conduction. Epicardial mapping of the atria at the time of cardiac surgery confirmed the presence of an anomalous left-sided connexion. After surgical section of the His bundle, complete antegrade AV block was produced with maintenance of intact retrograde conduction.

### Case report

The patient was a 44-year-old male Jehovah's witness, with documented recurrent paroxysmal supraventricular tachycardia for 15 years. Electrocardiograms between attacks were within normal limits, with a PR interval

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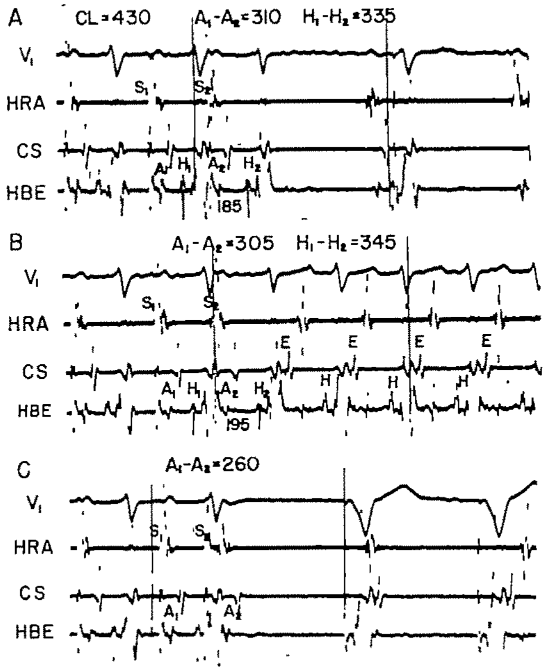

FIG. 1 *Induction of paroxysmal supraventricular tachycardia during coupled right atrial pacing at a basic cycle length of 430 ms. In panel A, the $A_1$-$A_2$ coupling interval is 310 ms. $A_2$ is conducted to the ventricles with an AH interval of 185 ms. In panel B, the $A_1$-$A_2$ interval has been decreased by 5 ms. $A_2$-$H_2$ interval is 195 ms and $A_2$ is followed by an echo beat (E) and an episode of paroxysmal supraventricular tachycardia is induced. Note that the coronary sinus (CS) electrogram of E precedes both high right atrial and low septal right atrial electrograms. In panel C, $A_1$-$A_2$ is 260 ms. $A_2$ is blocked in the AV node (proximal to H). The permanent ventricular pacemaker escapes following the blocked $A_2$.*

of 0·18 s, and a QRS duration of 0·08 s. Episodes of paroxysmal supraventricular tachycardia were characterized by rates of 170 to 190/minute and narrow QRS complexes identical to those noted during sinus rhythm.

During the two years before admission, attacks of paroxysmal supraventricular tachycardia had become more frequent and prolonged, occurring several times daily and often lasting for hours. The patient had to give up gainful employment as a lecturer because of the severity and frequency of the attacks. Therapy had included the following in high dosage, both singly and in combination: digitalis, propranolol, quinidine, phenytoin, and procainamide. The patient manifested refractoriness and/or major side effects to all of these drugs.

Because of failure of drug therapy, an attempt was made to control the tachycardia with atrial pacing, but was unsuccessful. A permanent externally activated demand epicardial ventricular pacemaker was implanted, when studies suggested that this mode of therapy would result in interruption of tachycardias. However, within several weeks of pacemaker implantation, intractable recurrent paroxysmal supraventricular tachycardia again occurred. The patient was then referred to the University of Illinois Hospital for further evaluation.

## Electrophysiological studies

Electrophysiological studies were performed in January 1975, after informed consent was obtained. Medicines were discontinued 72 hours before study. His bundle electrograms were recorded with catheter techniques (Scherlag *et al.,* 1969). In addition, a quadripolar catheter was positioned in the high right atrium for recording and stimulation. A hexapolar catheter was positioned so that the distal two poles were located at the right ventricular apex, while the proximal electrodes were contiguous to the low lateral right atrium. A bipolar catheter was placed in the distal coronary sinus.

Basic conduction intervals were recorded during sinus rhythm at a cycle length of 800 ms and were as follows: PA of 42 ms, AH of 84 ms, and HV of 45 ms. With high right atrial pacing, 1:1 AV conduction was noted up to a paced rate of 200/min, with an increase in AH interval from 110 to 200 ms. AV nodal Wenckebach periods were noted at a paced rate of 210/min. There was no evidence of an antegradely conducting anomalous pathway with pacing of the low lateral right atrium, the coronary sinus, and low septal right atrium (Denes *et al.,* 1974). With right ventricular pacing at rates of 90 to 170/min VA conduction (ventricle to low septal right atrium) remained constant at 230 ms. The sequence of atrial depolarization during retrograde conduction was distal coronary sinus, preceding both low septal right atrium and high right atrium by 40 ms.

Antegrade refractory periods were measured with atrial extra-stimulus technique from the high right atrium at cycle lengths of 600 and 430 ms and are listed in the Table. The AV conduction curves ($A_1$-$A_2$, $H_1$-$H_2$) were smooth.

TABLE *Refractory periods (ms)*

| *CL* | 600 | 430 |
|---|---|---|
| Atrial ERP | 220 | 230 |
| Atrial FRP | 270 | 250 |
| AV node ERP | 270 | 260 |
| AV node FRP | 380 | 330 |
| Ventricular ERP | — | 280 |
| Bypass ERP | | <280 |
| AV echo zone | | 305–270 |

CL = Cycle Length; FRP = Functional Refractory Period; ERP = Effective Refractory Period.

Retrograde refractory period determinations were performed using the ventricular extrastimulus technique ($V_2$) from the right ventricular apex at a cycle length of 600 ms. $V_2$-$A_2$ remained constant at 230 ms, despite shortening of $V_1$-$V_2$ from 580 to 285 ms. The sequence of atrial activation was identical to that described above during incremental ventricular pacing. VA conduction was limited by ventricular refractoriness at an $S_1$-$S_2$ interval of 280 ms.

Both single atrial echoes and sustained paroxysmal supraventricular tachycardia were noted during pacing-induced AV nodal Wenckebach periods, with achievement of a critical AH of 260 ms (Goldreyer and Damato, 1971). An echo zone (single echoes ± episodes of sustained paroxysmal supraventricular tachycardia) was defined with atrial extrastimulus technique between $A_1$-$A_2$ coupling interval of 305 to 270 ms at a cycle length of 430 ms (Fig. 1). The critical AH for induction of echoes during coupled stimulation was 195 ms (Fig. 1B) (Goldreyer and Damato, 1971).

Induced sustained paroxysmal supraventricular tachycardia was characterized by a narrow QRS, an HV of 45 ms, and a cycle length of 367 ms. Retrograde activation times during induced paroxysmal supraventricular tachycardia were as follows (measured from the onset of the QRS to the onset of the respective atrial electrogram): V-distal coronary sinus (110 ms), V-high right atrium (145 ms), and V-low septal right atrium (160 ms) (Fig. 1B).

Short periods of functional left and right bundle-branch block were also observed during episodes of induced paroxysmal supraventricular tachycardia. The cycle length during tachycardia with left bundle-branch block was always 25 ms longer than the cycle length during narrow QRS paroxysmal supraventricular tachycardia and with functional right bundle-branch block. Ventricular extrastimuli ($V_S$) were coupled to the QRS (V) of the tachycardia. At V-$V_S$ intervals greater than 345 ms, no reset of the atrial electrogram was noted. At V-$V_S$ intervals between 345 and 290 ms, the corresponding A to $A_S$ interval progressively shortened as the V-$V_S$ was decreased (Fig. 2). At V-$V_S$ intervals between 345-325 ms, the ventricular extrastimulus ($V_S$) depolarized the atria ($A_S$) without depolarizing the His bundle (Fig. 2A). At V-$V_S$ between 285 to 280 ms, $V_S$ depolarized the atrium and interrupted the tachycardia (Fig. 2C).

The presence of a left-sided concealed extranodal pathway with ability for only retrograde conduction was suggested by the following observations: 1) absence of antegrade pre-excitation on all electrocardiograms and during atrial pacing at multiple sites (Denes *et al.*, 1974). 2) Fixed V-A intervals during incremental and coupled ventricular pacing (Wellens and Durrer, 1974a; Narula, 1974). 3) Abnormal retrograde activation sequence (with distal coronary sinus preceding all other atrial electrograms) during ventricular pacing and during paroxysmal supraventricular tachycardia (Svenson *et al.*, 1974). 4) Lengthening of cycle length of paroxysmal supraventricular tachycardia during functional left bundle-branch block (Coumel and Attuel, 1974; Spurrell *et al.*, 1974a; Neuss *et al.*, 1975). 5) Ability to capture the atria from the ventricles during paroxysmal supraventricular tachycardia without depolarizing the His bundle (Zipes *et al.*, 1974; Neuss *et al.*, 1975). 6) Smooth antegrade AV nodal curves (Wu and Denes, 1975). During paroxysmal supraventricular tachycardia, the left-sided anomalous pathway was used for retrograde conduction and the AV node for antegrade conduction.

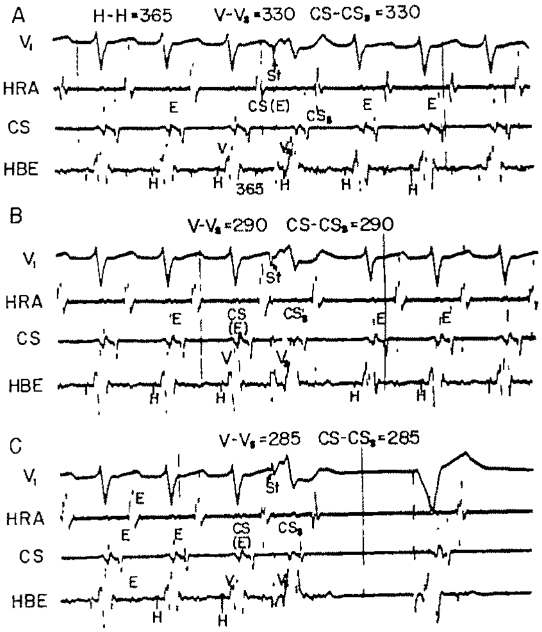

FIG. 2 *Atrial reset with premature ventricular stimulation during supraventricular tachycardia. V represents the last QRS before the introduction of the premature ventricular stimulus ($V_S$), CS represents the last coronary sinus electrogram before the ventricular extrastimulus. $CS_S$ represents the premature coronary sinus electrogram corresponding to the ventricular extrastimulus ($V_S$). E indicates echo and H represents the His electrogram. The cycle length of the tachycardia is 365 ms. Paper speed is 100 mm/s, time lines at 1/s.*

*Panel A: The V-$V_S$ is 330 ms. The corresponding CS-$CS_S$ interval is at 330 ms. Note that the HH intervals remain undisturbed at 365 ms. This shows that an extranodal pathway must be present. Panel B: The ventricular premature beat is introduced at a V-$V_S$ interval of 290 ms. The corresponding CS-$CS_S$ interval shortens to 290 ms.*

*Panel C: The V-$V_S$ interval is decreased to 285 ms; the corresponding CS-$CS_S$ interval is shortened to 285 ms and blocked in the AV node. The tachycardia is then interrupted. The ventricular pacemaker escapes with retrograde conduction to the atria.*

## Epicardial mapping and surgery

Because of medical intractability, and because of the demonstration of a circus movement amenable to correction, the patient was referred to the Texas Heart Institute for elective transection of the His bundle. Operation was performed in March 1975. With the heart exposed, epicardial mapping of the atria was performed during right ventricular pacing using a previously described mapping technique (Svenson *et al.*, 1974; Wyndham *et al.*, 1974). The area of earliest atrial activation was noted at the lateral left atrium just adjacent to the left AV ring (Fig. 3). The patient was placed on cardiopulmonary bypass, and the His bundle was interrupted via a right atriotomy incision. Atrial pacing after closure of the right atriotomy revealed complete AV block. Ventricular pacing after closure of the atriotomy revealed intact retrograde activation. Repeat epicardial atrial mapping with ventricular pacing was identical to that before operation.

## Subsequent clinical course

After operation, the patient recovered uneventfully. He has remained in heart block with pacemaker rhythm and he has been totally free of paroxysmal supraventricular tachycardia. He feels well and has resumed lecturing.

## Discussion

AV re-entry can occur within the AV node or using the normal pathway and an extranodal pathway (Coumel and Attuel, 1974; Denes *et al.*, 1973; Neuss *et al.*, 1975; Spurrell *et al.*, 1974a, b; Zipes *et al.*, 1974; Wellens and Durrer, 1974a; Svenson *et al.*, 1974; Wu and Denes, 1975). The extranodal pathway can be manifest with ability for antegrade conduction (Wolff-Parkinson-White syndrome) or concealed on the surface electrocardiogram. Concealment of an extranodal pathway reflects unidirectional block with ability for only retrograde conduction. The diagnosis of a concealed extranodal pathway can be suspected by demonstration of the following electrophysiological findings: 1) absence of antegrade pre-excitation on all electrocardiograms and during atrial pacing at multiple sites (Denes *et al.*, 1974). 2) Fixed ventriculoatrial conduction times during incremental and coupled ventricular pacing (Wellens *et al.*, 1974; Narula, 1974). 3) Abnormal sequence of retrograde atrial activation (Svenson *et al.*, 1974). 4) Increase in cycle length of induced paroxysmal supraventricular tachycardia during development of functional bundle-branch block ipsilateral to the suspected anomalous pathway (Coumel and Attuel, 1974; Spurrell *et al.*, 1974a; Neuss *et al.*, 1975). 5) Retrograde capture of the atria during paroxysmal supraventricular tachycardia without discharging the His bundle (Zipes *et al.*, 1974; Neuss *et al.*, 1975). 6) Smooth antegrade conduction curves ($A_1$-$A_2$, $H_1$-$H_2$) with echo zones (Wu and Denes, 1975).

All of the above electrophysiological features were shown in the present case, suggesting the presence

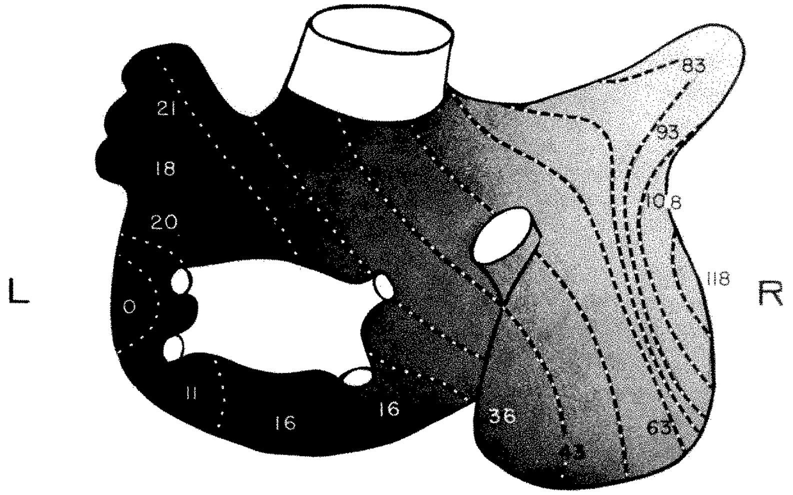

FIG. 3 *Posterior schematic view of epicardial atrial mapping during right ventricular stimulation.*

*Isochronous lines are drawn at 10-ms intervals with reference to the earliest epicardial atrial activation (0 ms). Note that the posterolateral left atrium contiguous to the left AV ring is activated earliest.*

of a concealed extranodal pathway. In addition, the findings suggested that the extranodal pathway was left-sided. The importance of our case resides in the fact that epicardial mapping of the atria confirmed the presence of a left-sided pathway, as predicted by preoperative electrophysiological studies. Epicardial mapping showed early retrograde activation of the lateral left atrium contiguous to the left AV ring.

Little is known regarding treatment of recurrent supraventricular tachycardia in patients with concealed extranodal pathways. In our experience, these cases are characterized by smooth conduction curves, as opposed to the discontinuous conduction curves often noted in patients with intra AV nodal (dual AV nodal pathway) re-entrant parosyxmal supraventricular tachycardia (Wu and Denes, 1975). Previous studies concerning induction of re-entrant tachycardia in the catheterization laboratory before and after drug administration suggest that patients with smooth conduction curves are more likely to have potentiation of induction after drugs which depress AV nodal conduction (ouabain and propranolol) (Wu *et al.,* 1974; Wu *et al.,* 1975). This probably reflects the fact that some of these smooth curve patients have concealed extranodal pathways underlying their paroxysmal supraventricular tachycardia (Wu and Denes, 1975). The administration of a drug depressing the AV node allows a given atrial extrastimulus to provoke greater AV nodal delays after drug administration. This additional delay potentiates the echo phenomenon, since the extranodal pathway is given more time for recovery from antegrade concealed penetration. Drugs such as procainamide and quinidine, which depress antegrade anomalous pathway conduction, should theoretically prolong retrograde refractoriness for the concealed pathway, so that these become incapable of sustaining re-entrant paroxysmal supraventricular tachycardia (Wellens and Durrer, 1974b). However, the present patient was unresponsive to procainamide and quinidine administration.

Both atrial and ventricular pacing have been used with varying degrees of success in the management of patients with intractable paroxysmal supraventricular tachycardia (Kitchen and Goldreyer, 1972). These were unsuccessful in the present case. The failure of ventricular pacing appeared to reflect the very narrow zone of coupling intervals (5 ms), in which a ventricular extrastimulus could interrupt sustained paroxysmal supraventricular tachycardia. Long periods of random ventricular pacing would be necessary before a random stimulus fell within this critical zone. Programming of a pacemaker to provide a stimulus in this zone could also fail, since it is likely that the zone might well change in timing from day to day.

Before the use of current diagnostic electrophysiological techniques, surgical cure of intractable paroxysmal supraventricular tachycardia had been achieved by destruction of the His bundle (Gianelly *et al.,* 1967). Surgery has also been used successfully in patients with manifest pre-excitation to interrupt re-entrant circus movements (Sealy and Wallace, 1974). Surgical ablation of anomalous pathway after demonstration with epicardial mapping can prevent recurrent circus movement paroxysmal supraventricular tachycardia (and also prevent rapid ventricular rates during paroxysmal atrial fibrillation). Similar cure of circus movement tachycardia has also been achieved in patients with pre-excitation occurring after surgical division of the normal pathway (Dreifus *et al.,* 1968; Wellens *et al.,* 1974).

This is the first reported case of a patient with intractable re-entrant paroxysmal supraventricular tachycardia caused by a proven concealed extranodal pathway cured by surgery. In this case, we chose to interrupt the His bundle, since this was the easiest of the possible procedures for achieving cure of the tachycardia. The fact that the patient was a Jehovah's witness and could not receive blood transfusions was another factor in reaching this decision. This operation had the disadvantage of producing chronic surgical heart block.

The other surgical approach to a case such as the present one would be to ablate surgically the concealed retrograde pathway. Theoretically, this would be ideal, since it would leave the normal conduction system intact without producing permanent heart block. However, technical difficulties might be anticipated in regard to localization of an anomalous pathway when this pathway was only capable of retrograde conduction. We believe that the feasibility of surgery for retrograde concealed pathways needs further exploration.

One additional point of interest relates to the current electrophysiological status of the present patient. He has chronic complete heart block with intact retrograde conduction. He thus resembles previously reported patients with chronic acquired complete heart block and intact retrograde conduction (Castillo and Samet, 1967; Goldreyer and Bigger, 1970). Previous authors have commented on the possibility that these patients have single lesions producing unidirectional heart block. The present case suggests that some patients with heart block and intact retrograde conduction have acquired heart block involving the normal pathway, with a concealed retrograde pathway allowing retrograde conduction.

We thank Dr. Bernard Kosowsky of St. Elizabeth's Hospital, Boston, for referring the patient, and Drs. Robert Hall and Denton Cooley for allowing us to perform the epicardial mapping at the Texas Heart Institute.

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# Angiographic demonstration of blood supply of right atrial myxoma[1]

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*A 53-year-old woman underwent cardiac catheterization for assessment of coronary arterial disease. An unexpected finding of a gradient between right atrium and right ventricle led to the discovery of an unsuspected right atrial myxoma. The diagnosis was established by the presence of a filling defect in the right atrial angiocardiogram and by the demonstration of 'tumour vessels' by selective right coronary angiography. Selective coronary angiography can visualize the blood supply to an intracardiac tumour and thus confirm the diagnosis preoperatively.*

Angiocardiography is the most definitive method for the diagnosis of intracavitary cardiac tumours (Steinberg *et al.*, 1964; Steiner, 1968). An atrial myxoma will be demonstrated as a filling defect in an atrial angiocardiogram. The distinction must be made between tumour, thrombus, and artefact caused by streaming (Steiner, 1968). The visualization of an abnormal blood supply to the region of the filling defect would support the diagnosis of a filling caused by a tumour. Such 'tumour vessels' have been described (Marshall, Steiner, and Wexler, 1969). To our knowledge this is the first case in which the blood supply to a right atrial myxoma has been demonstrated by selective right coronary arterial injection.

## Case report

A 53-year-old woman was admitted to hospital in August 1974 for assessment of angina pectoris. She was well until 1969 when she had a documented anterior wall myocardial infarction. After this infarction she developed disabling typical angina pectoris precipitated by minimal exertion. She was subsequently referred for selective coronary arteriography and consideration for aorto-coronary vein graft bypass surgery. Before that, between 1969 and 1972, she had had several episodes of severe left praecordial chest pain with characteristic electrocardiographic abnormalities of pericarditis; she was treated with cortisone and aspirin which provided control of this chest pain.

She also complained of recurrent episodes of rapid palpitations documented as atrial tachycardia since 1972. These episodes were usually precipitated by mild exertion and excitement, though they occurred occasionally at rest. Relief was obtained by the Valsalva manoeuvre or carotid pressure and the episodes were largely controlled after institution of digitalis therapy. On one occasion, shortly before admission, she had a syncopal episode associated with rapid palpitations and nausea. The duration was a few minutes and there were no recurrences.

She also had four episodes of left hemiparesis and hemianaesthesia lasting one and one-half to three hours over a 10-day interval, one month before admission.

Past history included hypertension for 17 years. The family history was positive for rheumatic fever in both parents and for hypertension in her father.

Physical examination revealed a white 53-year-old woman looking younger than her stated age. The fundi showed grade II hypertensive retinopathy. Examination of the neck and chest was unremarkable. The blood pressure was 160/110 mmHg (21·3/14·6 kPa) in the right arm, supine position. Both 'a' and 'v' waves of the jugular venous pulse were 2 to 3 cm above the sternal angle. Kussmaul's sign was negative. There was a slight sternal lift and a prominent left ventricular impulse with the apical impulse 3 cm lateral to the midclavicular line.

On auscultation the first and second heart sounds were normal. At the apex a fourth heart sound was heard. A presystolic and systolic 'rub' were audible at the lower left sternal border. The remainder of the physical examination was unremarkable.

### Cardiac catheterization

Right and left heart catheterization were performed

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[1] This work supported in part by Canadian and Ontario Heart Foundation grants.

percutaneously via the right femoral artery and vein. A second venous catheter was subsequently introduced into the right femoral vein. Pressures were recorded by Statham p23 Db transducers and an Electronics for Medicine Recorder. Right atrial angiograms were performed via a N.I.H. angiocatheter using 50 ml Renografin-76. A left ventriculogram was performed with 50 ml Renografin-76 via the retrograde catheter. Selective coronary angiograms were performed by Judkin's technique.

## Results

There was a large apical aneurysm. The remainder of the left ventricle contracted normally.

The left anterior descending artery was totally occluded at its origin. The coronary arteries were otherwise free of obstructive diease.

On withdrawal from right ventricle to right atrium, a pressure gradient was noted. This was confirmed by simultaneous right atrial and right ventricular pressure recordings. The 'a' wave gradient was 14 and the integrated gradient 8 mmHg (1·1 kPa). The right atrial angiogram showed a large filling defect moving back and forth across the tricuspid orifice (Fig. 1). Selective right coronary angiogram indicated clusters of small tortuous vessels, pooling, and a 'tumour blush' arising from the right coronary artery in the region of the right atrium (Fig. 2a). The repeat selective angiogram, four weeks after operation (Fig. 2b) showed the absence of this abnormal group of vessels.

At operation, the tumour had the typical appearance of a myxoma and this was confirmed histologically.

## Discussion

Although uncommon (Heath, 1968), myxomas are important because they represent potentially lethal lesions amenable to surgical cure (Greenwood, 1968; Firor, Aldridge, and Bigelow, 1966). The diagnosis is difficult because of the wide variety of potential manifestations (Greenwood, 1968; Harvey, 1968; Aldridge and Greenwood, 1960). Angiography has been the most reliable diagnostic tool but false positives occur fairly commonly (Steiner, 1968). When a filling defect can be shown, the distinction must be made between tumour, thrombus, and artefact caused by streaming.

Echocardiography has been shown to be useful for confirming the presence of atrial myxoma particularly of the left atrium, but the echocardiographic diagnosis of right atrial myxomas has been described

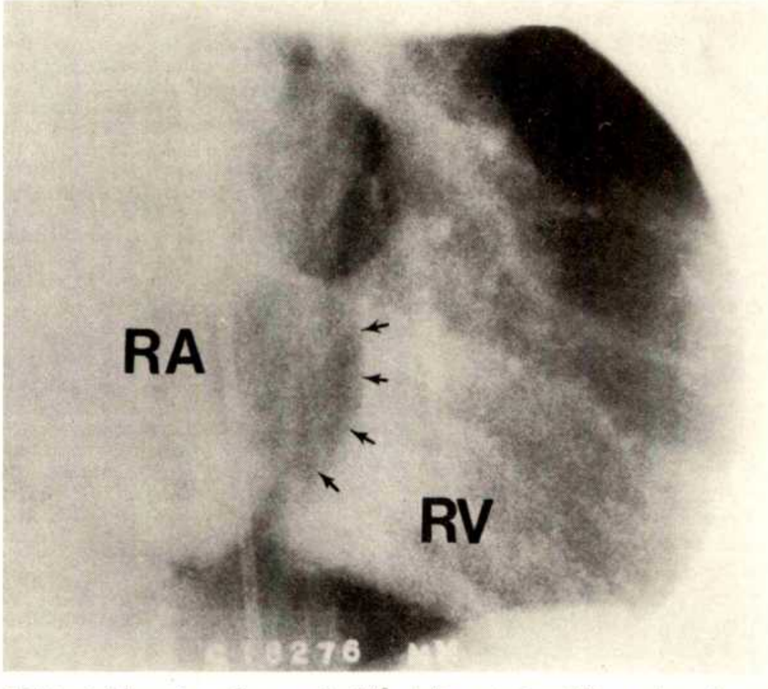

FIG. 1 *Right atrial angiocardiogram in 30° right anterior oblique view. Arrows indicate edge of filling defect. RA—right atrium, RV—right ventricle.*

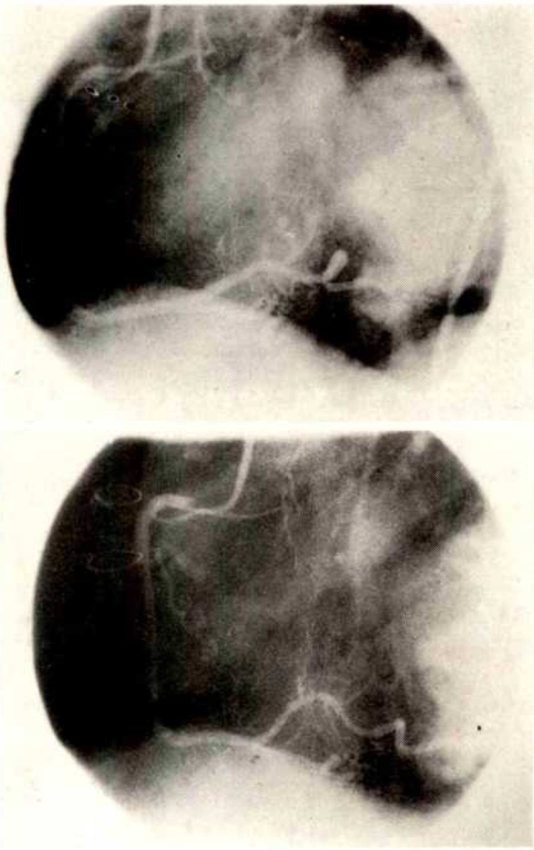

FIG. 2 *Selective right coronary angiograms in left anterior oblique projection. a) Preoperative: small tortuous vessels and lacunae can be seen near the bifurcation. b) Postoperative: previously noted abnormal vessels can no longer be seen.*

(Wolfe, Popp, and Feigenbaum, 1969; Waxler, Kawai, and Kasparian, 1972; Harbold and Gau, 1973). This appears to require a large tumour that prolapses deeply into the right ventricular cavity (Harbold and Gau, 1973). In this case, even a retrospective echocardiogram failed to demonstrate any abnormality though the anterior leaflet of the tricuspid valve was not well visualized.

The patient presented above was investigated primarily for assessment of coronary artery disease. During routine catheterization, a diastolic gradient was noted between right atrium and right ventricle. To clarify the cause of this gradient (valvular, tumour, thrombus, etc.), a right atrial angiocardiogram was performed which indicated a filling defect moving back and forth through the tricuspid orifice. The suspicion of right atrial myxoma was confirmed when the selective right coronary angiogram showed an abnormal group of blood vessels in the region of the defect. The histology of the surgically removed tumour was that of a typical myxoma (Heath, 1968; Hudson, 1965). In view of the vascularity associated with most myxomas, one would anticipate that visualization of this vascularity could be readily performed to aid in the diagnosis. This has been described in a few cases of left atrial myxoma (Marshall *et al.*, 1969; Chan, 1974), but not to our knowledge with right atrial myxoma.

Most patients in whom myxomas have been documented angiographically have not had selective coronary angiograms performed. This case illustrates that a selective coronary angiogram may be useful to confirm the diagnosis of myxoma or other intracardiac tumour and help distinguish between tumour, thrombus, and artefact.

Similarly, most patients having selective coronary angiograms do not have atrial angiocardiograms. If the coronary angiograms show an abnormal group of vessels as documented here, these patients should have further angiography to assess the possible presence of an intracardiac tumour.

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# Electrical alternans of TU wave in Romano-Ward syndrome

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*A case is presented in which an exceptional electrical alternans of the TU wave occurred in association with the Romano-Ward syndrome. This appears to be the first reported example of this association. Ventricular fibrillation was documented during the syncopal attacks. There was no evidence of abnormality of the serum electrolytes.*

Electrical alternans of a single wave on the electrocardiogram is uncommon, and in particular TU or U wave alternans is an extremely rare phenomenon. The electrophysiological mechanism responsible for it has not been well defined. The following case with the Romano-Ward syndrome shows TU wave alternans without changes in the QRS complex.

## Case report

A 67-year-old woman was admitted to hospital on 20 May 1971 after experiencing several syncopal episodes. The attacks first started when she was a schoolgirl. Since the age of 20 she had experienced syncopal attacks while taking a bath. For a few days before admission she had fever, increased frequency of micturition, and syncopal attacks, with convulsions at times.

On admission she was confused and had a temperature of 38°C. The blood pressure was 150/90 mmHg (20/12 kPa). Convulsions occurred suddenly, with facial cyanosis and incontinence. The attacks lasted for a few minutes. Physical examination in the conscious state was within normal limits except for spinal scoliosis. Chest radiographs and encephalograms were normal. Laboratory examinations showed a slightly disturbed liver function (AST, 68, ALT, 75, and LD 430 units) and renal function (BUN 45 mg/dl), and mild anaemia (red blood cells $3{\cdot}4 \times 10^{12}$/l; white blood cells $3{\cdot}5 \times 10^{9}$/l; and a haemoglobin 12 g/dl. All serum electrolytes including Na, K, C1, Ca, and phosphate were within normal limits. Urinalysis showed a trace of albumin, 1+ sugar, 14–17 red blood cells and many white blood cells per high-power field. Urine culture showed *Pseudomonas aeruginosa* and Gram-positive bacilli, from which a diagnosis of acute urinary tract infection was made.

An electrocardiogram taken during the attacks showed ventricular fibrillation (Fig. 1). On the second day in hospital the TU wave alternans was recorded (Fig. 2). There was no change in the QRS complex. The interpretation of this finding is discussed below.

Although the patient was free from any syncopal attacks during hospitalization except on the day of admission, phenobarbitone, ajmaline, and theophylline-ethylenediamine were administered for the convulsive attacks. She was also treated for acute urinary tract infection with kanamycin and nalidixic acid. The laboratory data improved considerably and she was discharged on 23 June 1971, but subsequently seen at intervals thereafter.

Electrocardiagrams recorded at various times are shown in Fig. 3; there appear to be prolonged QT intervals in Fig. 3A and 3C, with no definable U wave. In Fig. 3B leads I, II, III, and aVF appear to show QT prolongation, but leads V3, V5, and V6 show a prominent U wave, suggesting that the delayed repolarization wave in leads I, II, and III is a combined TU wave.

The patient's family history was as follows. She was the eldest of eight sibs and only the second sister is alive besides the patient. The QT interval on her electrocardiogram was also prolonged, being 0·47 s. Six other sibs and both parents died of diseases unrelated to syncopal attacks. The family of the mother's sister, whose spouse was a cousin of the patient's father, is worth noting. She had seven children. Three of them died suddenly at the ages of 2 to 3; one of them died suddenly on a public transport vehicle. Three others grew up and are living, and one of them is now in a provincial hospital (Fig. 4).

## Discussion

Jervell and Lange-Nielsen (1957) first described a syndrome consisting of congenital deaf-mutism, prolongation of the QT interval, syncope, and

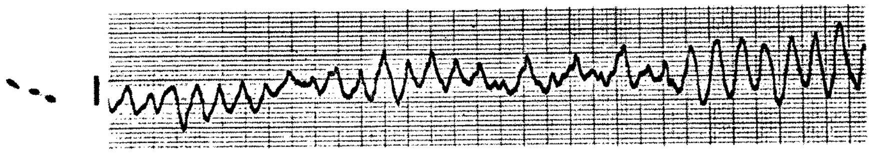


FIG. 1 *Ventricular fibrillation during syncopal attacks.*

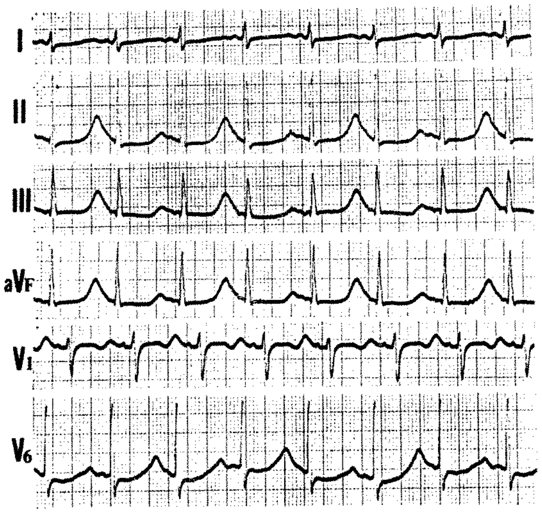


FIG. 2 *An electrocardiogram obtained on the day after admission. TU wave alternans is conspicuous.*

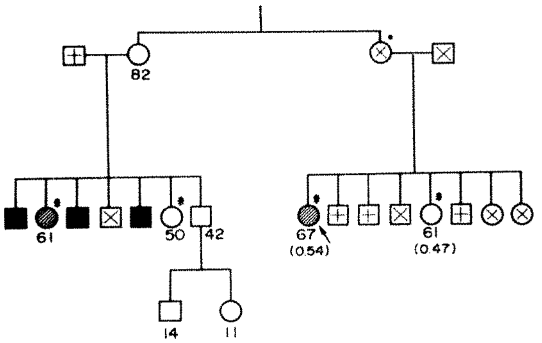
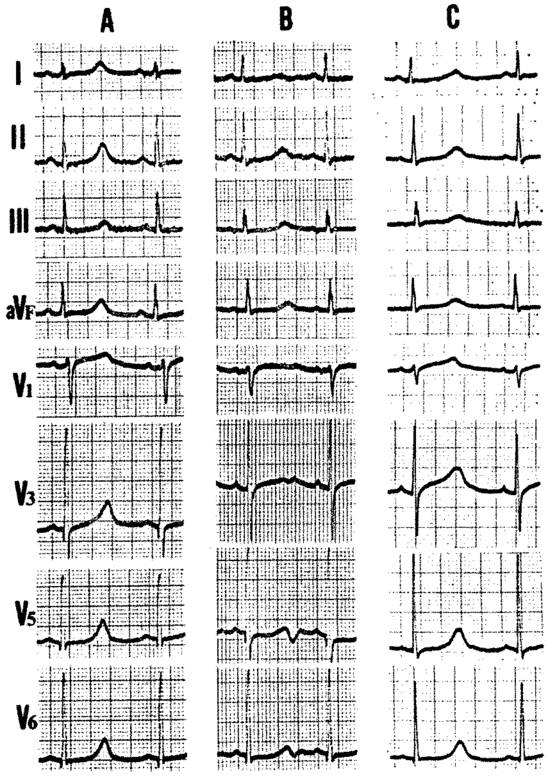


FIG. 4 *Pedigree of the family of our case. Numbers denote age in years and figures in parentheses the QTc interval. The arrow indicates the propositus. Symbols are as follows:*

* *unmarried;* • *hypertensive;* ⊞ *died of pulmonary tuberculosis;* ■ *died suddenly;* ⊠ *or* ⊗ *died of other causes; and* ▨ *history of syncopal attacks.*



15–6–1971 21–7–1971 4–9–1973

FIG. 3 *Changes of T or TU wave. For details see text.*

sudden death. Later, Romano, Gemme, and Pongiglione (1963) and then later Ward (1964) reported on a similar syndrome characterized by QT prolongation, syncope, and sudden death but unassociated with deaf-mutism. In both cases QT prolongation was caused neither by extracellular hypopotassaemia nor by hypocalcaemia. It is evident that there is more clinical significance in the latter syndrome than in the former in that the syncope or sudden death occurs in apparently otherwise healthy children or adults. As regards heritable QT prolongation without deaf-mutism, the so-called Romano-Ward syndrome, 20 families consisting of 85 affected members have been reported to date (Hiejima, 1975).

In the case observed by us there had been repeated attacks of syncope since childhood, prolongation of the QT interval not due to the abnormal extracellular electrolytes, and familial occurrence of syncope and sudden death. Accordingly, there seems to be little doubt that the present case represents an example of the Romano-Ward syndrome. In addition the patient showed a transient alternation of the TU or the U wave. Alternating variation of the T wave can be seen in Fig. 5 of Romano *et al.* (1963), where alternate beats show upright and inverted delayed T waves.

The identification of the wave showing alternans as a U wave was based on Lepeschkin's criteria (1969): (1) The wave in question appears extremely late in diastole in leads II, III, and AVF. Lepeschkin published a nomogram showing the time relation between the apex of the T and that of the U at different Q-Q intervals. Employing this, we considered the apex of the wave in question could be that of the U wave. However, it is difficult to be certain that it is in order to apply the Lepeschkin nomogram to this patient in the absence of any method by which a pathologically delayed T can be separately identified from the U. (2) When the electrogram of Fig. 3A was taken, a phonocardiogram was also recorded (not shown). In simultaneously recorded lead II the apex of the wave in question appeared 0·01 s before the beginning of the second heart sound. Lepeschkin stated that, if the apex of a questionable wave appears before the second heart sound, it is part of the T wave, whereas if it appears later than 0·03 s after the beginning of the second heart sound it is almost certainly formed by the apex of a U wave. Consequently the wave in question in Fig. 3A is a T wave. In contrast a wave with two positive peaks is seen in leads V3 and V5 in Fig. 3B. The second peak of these waves is unlikely to be a T wave but most likely to be a U wave, since they appear later than the peak of the wave now considered to be a T wave in Fig. 3A in spite of the shorter Q-Q interval. Particularly in lead V5 the interval between these two apices is 0·16 s. According to Lepeschkin the apices of diphasic T wave are usually less than 0·15 s apart, whereas the interval between the T and U apices is usually greater than 0·15 s. Therefore, the second peak in lead V5 is consistent with the U wave. At the time of the recording of the tracing on 21 July 1971 the patient clearly had a U wave, which was not easily identified separately in other tracings. On this account it is suggested that the peak of the wave showing alternans in Fig. 2 may also be the U wave, and the repolarization wave in V1 suggests that an inverted T component may precede U waves of alternating high and low amplitude. The wave showing alternans may therefore be either a U wave or a complex TU.

The occurrence of the TU or U wave alternans is an exceptionally rare phenomenon. To our knowledge there is only one such report, by Bashour, Rios, and Gorman (1973). Their case resembles ours closely and shows a huge U wave alternans. They did not mention, however, why they regarded the alternated wave as the U wave. Furthermore, the apex of the wave showing alternans in their case (their Fig. 2) appeared earlier than in our case. Though the interval from the beginning of the QRS complex to this apex was almost equal (0·48 s), there was a difference in the Q-Q interval (0·76 s in their case against 0·68 s in ours). The superimposition of T wave alternans cannot be excluded either. Though ventricular fibrillation was also observed in their case, the case is not consistent with the Romano-Ward syndrome, because there were moderate hypomagnesaemia, mild hypocalcaemia, and absence of familial occurrence. Fraser, Froggatt, and James (1964) described a change of the repolarization wave which occurred after the patient became extremely apprehensive. The wave in Fig. 11B and C of their paper might be similar to ours because of its late appearance, though they seemed to regard it as a T wave. However, they did not mention it as an electrical alternans. The rhythm and shape of the waves are not exactly regular. The strip is too short to determine whether it is a U wave alternans or not. Accordingly, our paper seems to be the first report of the TU wave alternans in the Romano-Ward syndrome.

Scherf and Bornemann (1971) described a larger U wave in the first beat after a pause as a constantly recurring pattern in various arrhythmias. Mullican and Fisch (1964) described a case showing postextrasystolic alternans of the U wave. Ten patients with left ventricular failure and postextrasystolic U wave alternans were reported by Eyer (1974). Kimura and Yoshida (1963), Ricketts, Denison, and Haywood (1969), and Dolara and Pozzi (1971) each reported on a case of the T wave alternans. Whether these are due to a similar mechanism or not cannot be determined, since it is not yet clear whether the U wave is a reflection of the Purkinje system repolarization, of afterpotential, or of any other events.

Experimental studies by Kleinfeld, Stein, and Kossmann (1963) suggested that alternation in the rate and extent of calcium and potassium transport across the myocardial cell membrane was responsible for T wave alternans. The problem of electrical alternans of the T wave has been further discussed by Schwartz and Mallini (1975), who ascribe the changes to asymmetrical sympathetic stimulation of the right and left sides of the heart, a mechanism which has been invoked by Yanowitz, Preston, and Abildskov (1966) to account for the basic QT prolongation in the syndrome. Mullican and Fisch (1964) ascribed their finding on the post-extrasystolic alternans of the U wave to hypopotassaemia. Bashour *et al.* (1973) attributed the U wave abnormality of their case to hypomagnesaemia with possible additional influence from concomitant hypocalcaemia. Ward (1966) examined the serum electrolytes before and after the exercise-induced attacks of syncope, and found that no gross change occurred in the extracellular electrolytes. Furthermore Johansson and Jorming (1972) gave their patient potassium chloride and magnesium sulphate intravenously and calcium acetate orally without effect. In our case all those electrolytes examined were within normal limits. The magnesium content of the blood was not examined, unfortunately.

Fraser *et al.* (1964) supposed that the prolongation of the QT interval in the Jervell-Lange-Nielsen syndrome was induced by a diffuse cardiac metabolic error suggested by lack of characteristic clear zone and bulge of the Purkinje fibres at necropsy. The mechanism of the prolongation of the QT interval in the Romano-Ward syndrome has not been fully elucidated yet.

Ventricular irritability has been emphasized in the Romano-Ward syndrome and ascribed to the prolongation of the QT interval. Han and Moe (1964) stated that temporal dispersal of repolarization may lead to instability during repolarization, or alternation may lead to a circus movement that may provoke ventricular fibrillation. There may be more chance of the premature beat hitting the vulnerable period of the preceding beat. Wellens, Vermeulen, and Durrer (1972) did not find greater differences in functional refractory period at different sites in right and left ventricle at different driving rates. Their patient showed a considerable U wave, which made it impossible to determine the true length of the QT interval. The QT was considered to be normal at rest, but after auditory stimulation it became prolonged, and the case probably belongs to the Romano-Ward category, which makes the observation of the absence of a variation in refractory periods in different areas of the heart muscle relevant to this discussion.

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*British Heart Journal*, 1976, **38**, 771–772.

# Ventricular tachycardia with retrograde conduction
## *Simplified diagnostic approach*

Sir:

In the article by Evans *et al.*, 1974, **36,** 512–515) some statements are misleading, and their message, if accepted, will represent a retrogressive step in the diagnosis of arrhythmias. Four of their assertions invite critical comment:

1) 'The diagnosis of ventricular tachycardia is primarily dependent upon the demonstration of dissociated atrial and ventricular activity.'

The urge to find independent atrial activity is a symptom of the 'P-preoccupation syndrome', a disease endemic among cardiographers at all levels of sophistication. For many years those conversant with the diagnosis of arrhythmias have emphasized that AV dissociation is *not* a valid point in distinguishing ventricular tachycardia from supraventricular tachycardia with aberration. The diagnosis is not 'primarily dependent' on this inadequate clue, and its use is as scientifically acceptable as to assume that the woman on the man's arm is his wife. AV junctional tachycardia with aberration may be dissociated from the atrial rhythm; and ventricular tachycardia may be associated with 1:1 retrograde conduction. Neither does dissociated atrial activity prove nor does constantly related atrial activity disprove ventricular tachycardia. Better clues are required and, in recent years, the value of morphological QRS detail has been stressed; certain features, *when present,* can be of great diagnostic value.

2) 'When ventricular tachycardia occurs with intact retrograde conduction the distinction between supraventricular tachycardia with aberrant conduction and ventricular tachycardia with retrograde conduction is considered almost impossible to make.'

If an, at best, inadequate clue—AV dissociation—is depended upon, obviously diagnosis is rendered impossible by retrograde conduction. But morphological detail, on the other hand, with or without retrograde conduction is equally discriminating. With its help the diagnosis, far from being 'almost impossible', is sometimes extremely easy.

3) 'The presence of a right bundle-branch block pattern, particularly when triphasic, supports a diagnosis of supraventricular tachycardia with aberrant ventricular conduction.'

They are correct in their assertion about a triphasic pattern; but if by 'RBBB pattern' these authors mean, as many do, any pattern with a wide dominant positive wave in V1 then their statement is incorrect and the facts are: 1) statistically a monophasic (R) or diphasic (qR) pattern is more likely to represent ectopy than aberration; and 2) if such a complex peaks early (taller left than right 'rabbit-ear') the odds are strongly (at least 80%) in favour of ventricular ectopy.

4) '. . . the proven diagnosis of ventricular tachycardia.'

Their diagnosis was not by any means proven by their 'simple approach'; their manoeuvre, by producing retrograde VA block and eliminating P waves, excluded an atrial but not junctional origin of the tachycardia and was no more diagnosistic than would be the demonstration of independent atrial activity.

In fact, the most compelling evidence in favour of ventricular tachycardia in *this* case is morphological: the QRS complexes are predominantly negative across the praecordium. This is a *simpler* approach (requiring only a glance at a 12-lead tracing) and a more convincing clue than the still equivocal evidence the authors have acquired by dint of atrial invasion plus vagal stimulation —procedures that are usually unnecessary and not without risk in the presence of acute infarction and an irritable myocardium.

The most important point is that the reader of Evans's article should not be beguiled into believing that an inadequate clue, sought if necessary by invasive means, is the primary target in the diagnosis of ventricular tachycardia.

To forestall the possible riposte that I too have been guilty of emphasizing the diagnostic value of independent atrial activity, let me hasten to acknowledge that in 1963—12 years ago when neither I nor anyone else knew any better—I stated that independent P waves were of prime importance in the diagnosis of ventricular tachycardia (Marriott, 1963). But, during the past decade, a wealth of knowledge has accumulated about QRS morphology—triphasicity in V1 and V6, 'rabbit ears' in V1, rS or QS in V6, concordant praecordial positivity and negativity, bizarre frontal plane axis, wide r in V1, etc.—and reliance on independent atrial activity is now a relic of former less enlightened times. Morphological clues are not always present; but when they are they afford much more diagnostic evidence than independent atrial activity.

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## Reference

Marriott, H. J. L. (1963). *Armchair Arrhythmias*. Tampa Tracings, Cardiology Center, Tampa General Hospital, Tampa, Florida.

Sir:

Dr. Marriott criticizes our statement that the 'Diagnosis of ventricular tachycardia is primarily dependent upon the demonstration of dissociated atrial and ventricular activity'. He asserts that this is an inadequate clue, 'as scientifically acceptable as to assume that the woman on the man's arm is his wife'. This statement closely resembles one in an article entitled 'AV dissociation revisited' by Marriott and Menendez (1966). However, in 'Armchair arrhythmias' Marriott (1963) makes two different statements. Speaking on ventricular aberration, he says (p. 7), 'These common pitfalls are avoided by keeping in mind the golden rule in the diagnosis of arrhythmias in general, *cherchez le P*. Marriott goes on to say (p. 20) that, 'The clues to diagnosis (ventricular tachycardia) are provided by the signs of AV dissociation (independent beating of atria and ventricles). In the electrocardiogram, the dissociation can be recognized and the ventricular origin inferred *only* if independent P waves are visible or "Dressler beats" are present.' These latter views of Marriott concur with our statement and the views of many other experts. Marriott's several other points all stress the significance of QRS morphology in the recognition of ventricular tachycardia. We share, and discussed in our article, his views on the value of the triphasic QRS (right larger than left rabbit ears) supporting aberrancy. The absence of this finding may indeed favour ventricular origin, but certainly is not diagnostic, and particularly in a patient with a healed anterior wall myocardial infarct and ventricular aneurysm one would not rely on praecordial QRS morphology for diagnosis.

Although our patient did not have an acute myocardial infarction, as Marriott inferred, we concur that invasiveness in an acute ischaemic situation is hazardous. However, the hazards of recording an intra-atrial electrocardiogram in an electrically safe fashion are not only trivial, they are far less risky than many of the stresses to which our myocardial infarct patients are subjected. On the other hand, to make the distinction between ventricular tachycardia with intact retrograde conduction and junctional tachycardia with aberrancy and retrograde conduction requires high-risk ventricular invasion for His bundle recordings. The wiser part of valour when confronted with this differential, with or without the setting of an acute myocardial infarction, is to presume the more virulent process—ventricular tachycardia.

In summary, we are somewhat puzzled by Dr. Marriott's disparaging remarks regarding the value of P wave analysis. While we concur with his thoughts on the *potential* value of QRS morphology, we can think of several instances when this would be of little value or no value such as in our patient with an old anterior wall myocardial infarction and a healed ventricular aneurysm.

In actuality, in the clinical setting, the goal is to distinguish supraventricular tachycardia with aberrancy from either ventricular tachycardia or junctional tachycardia with aberrancy. In fact, junctional tachycardia with aberrancy is most often empirically treated as ventricular tachycardia unless immediate His bundle recordings can be obtained.

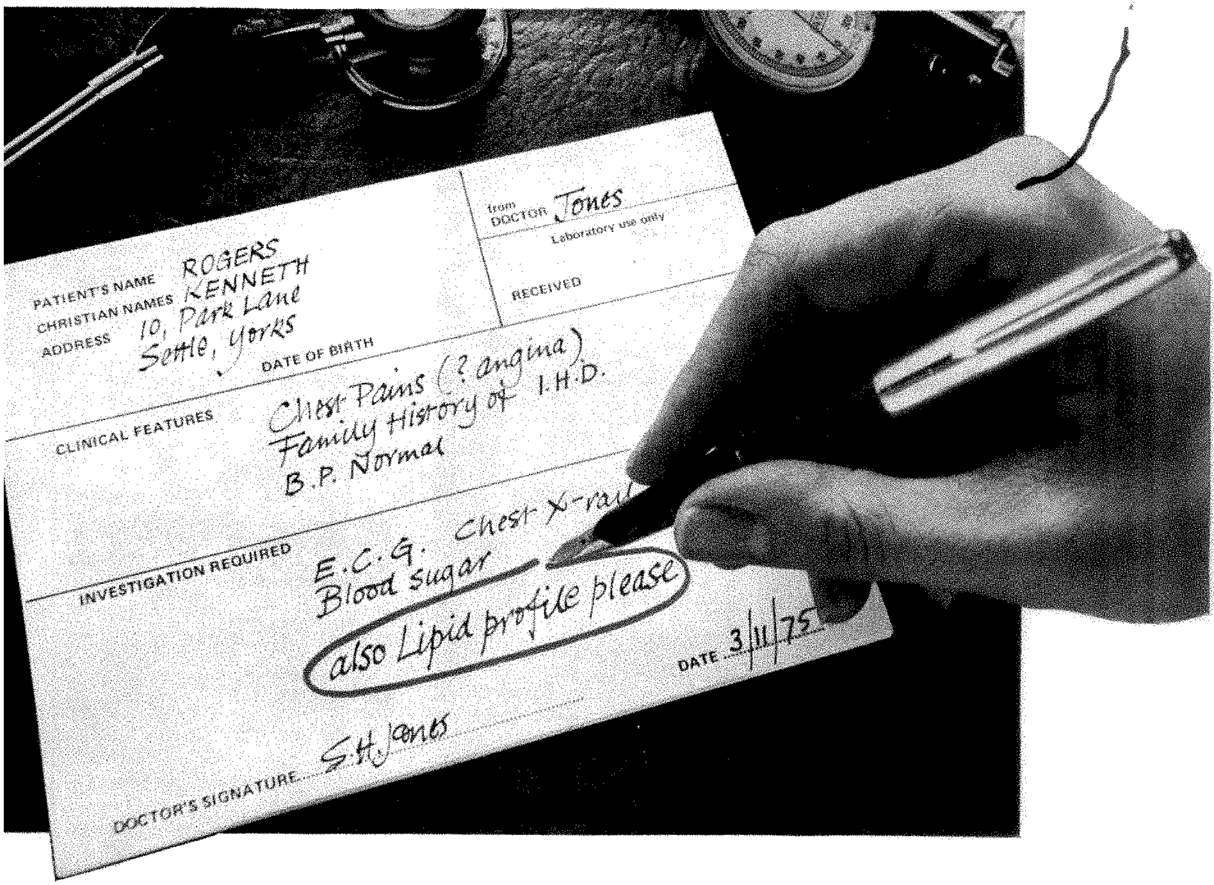
Despite Dr. Marriot's desire to shed his valuable contributions of the past, we still support them and remain imbued with the philosophy of Willie Sutton, a notorious Boston bank robber, who when asked why he robbed banks, replied: 'That's where the money is'. Analysis of the atrial electrical activity (*cherchez le P*) often detectable only in the atrium, is 'where the money is' in arrhythmia diagnosis.

Gerald L. Evans,
Framingham Union Hospital,
25 Evergreen St.,
Framingham, Mass., U.S.A.

## References

Marriott, H. J. L. (1963). Armchair arrhythmias. In *Tampa Tracings*. Cardiology Center, Tampa General Hospital, Tampa, Florida.

Marriott, H. J. L., and Menendez, M. M. (1966). AV dissociation revisited. *Progress in Cardiovascular Diseases*, 8, 522.



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B.P. Normal

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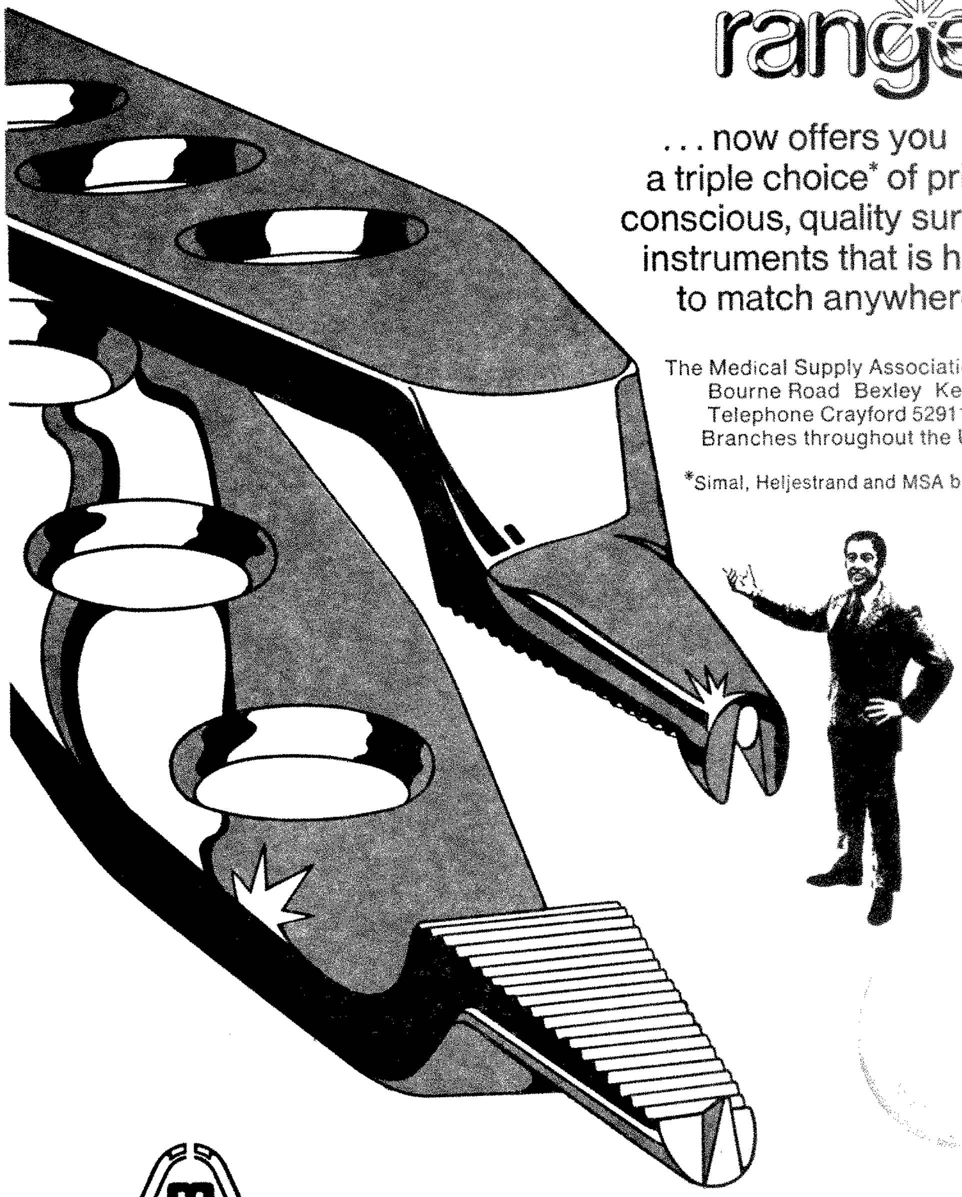

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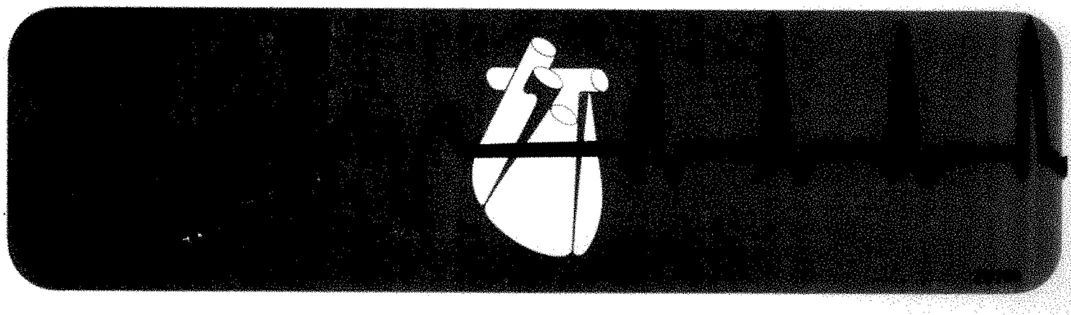

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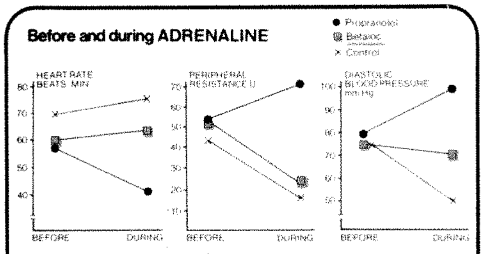

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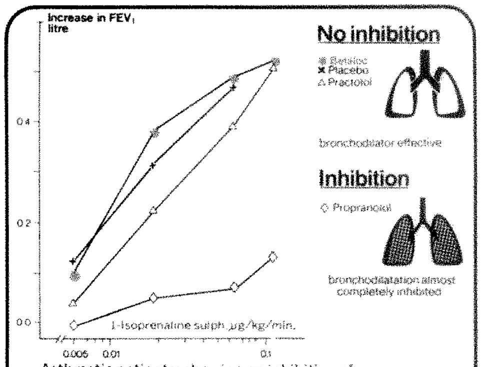

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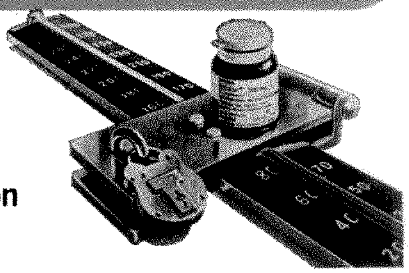

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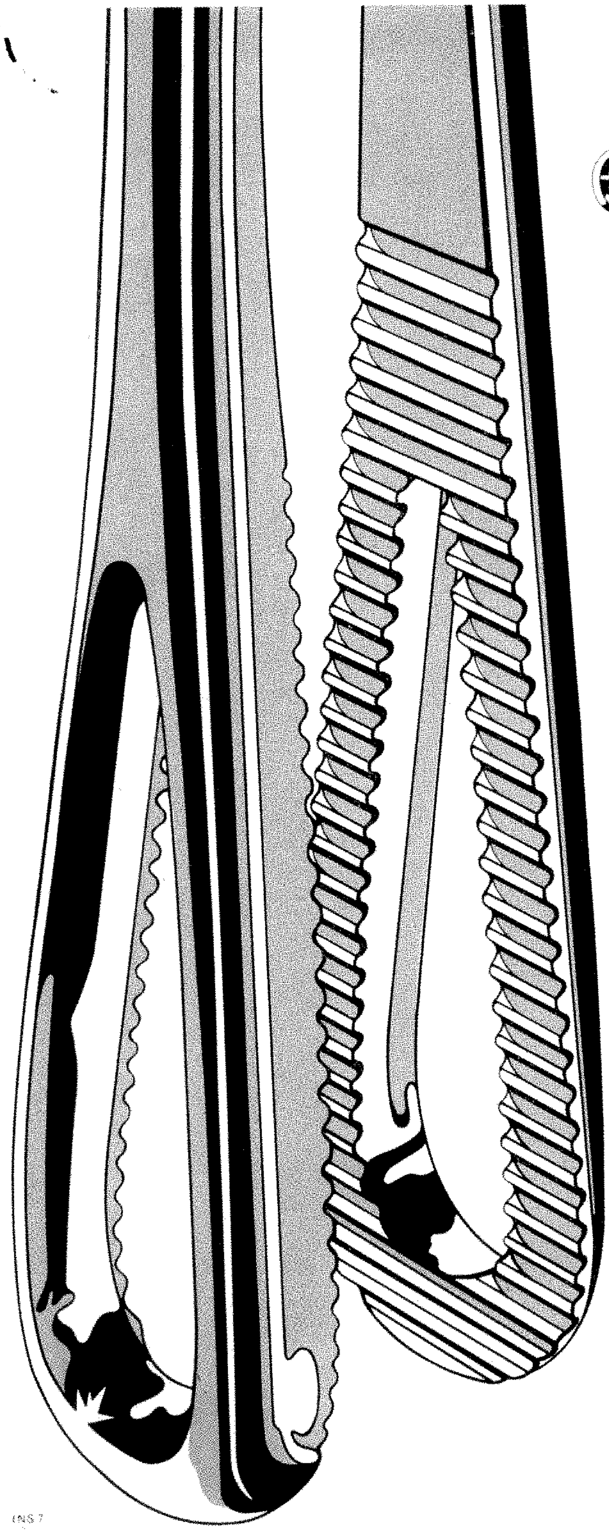

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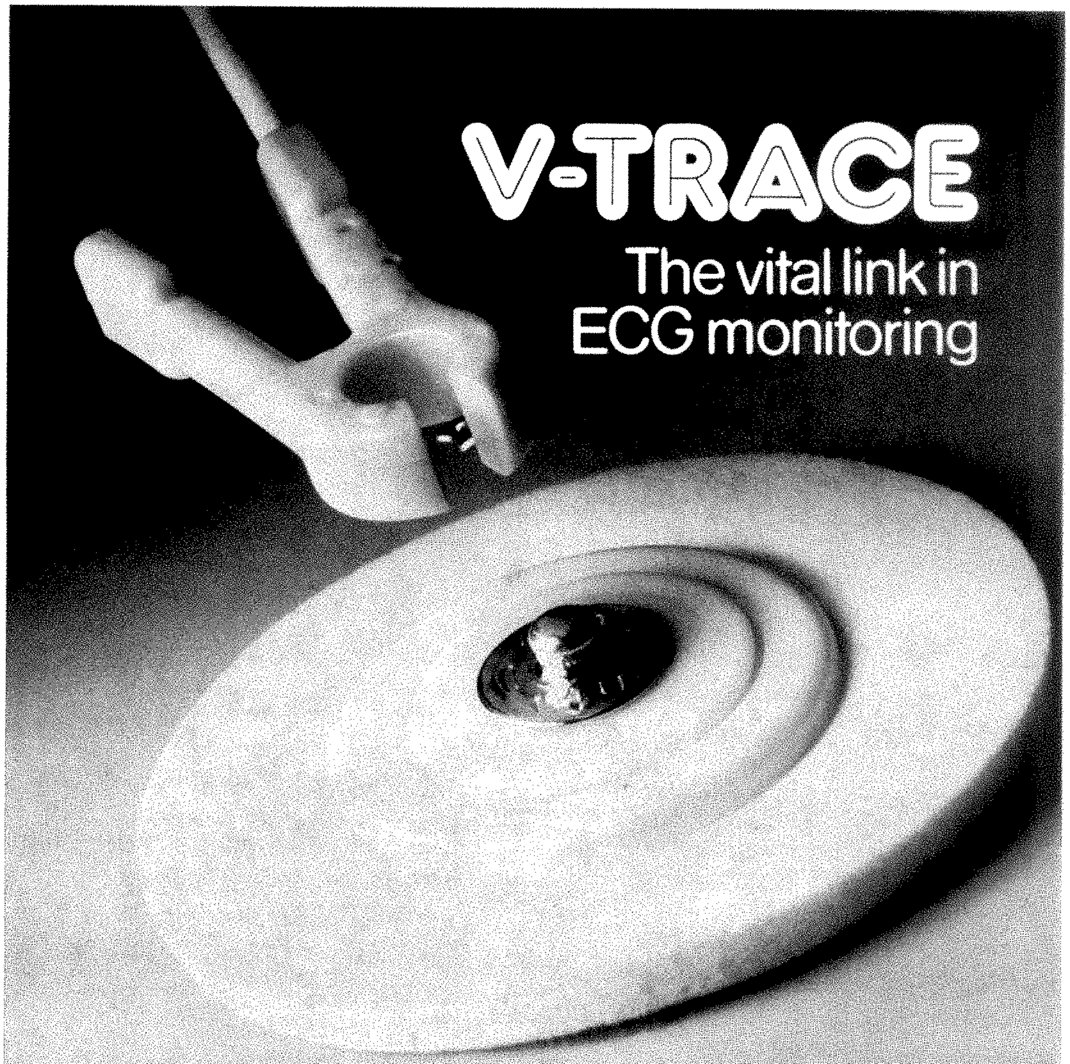

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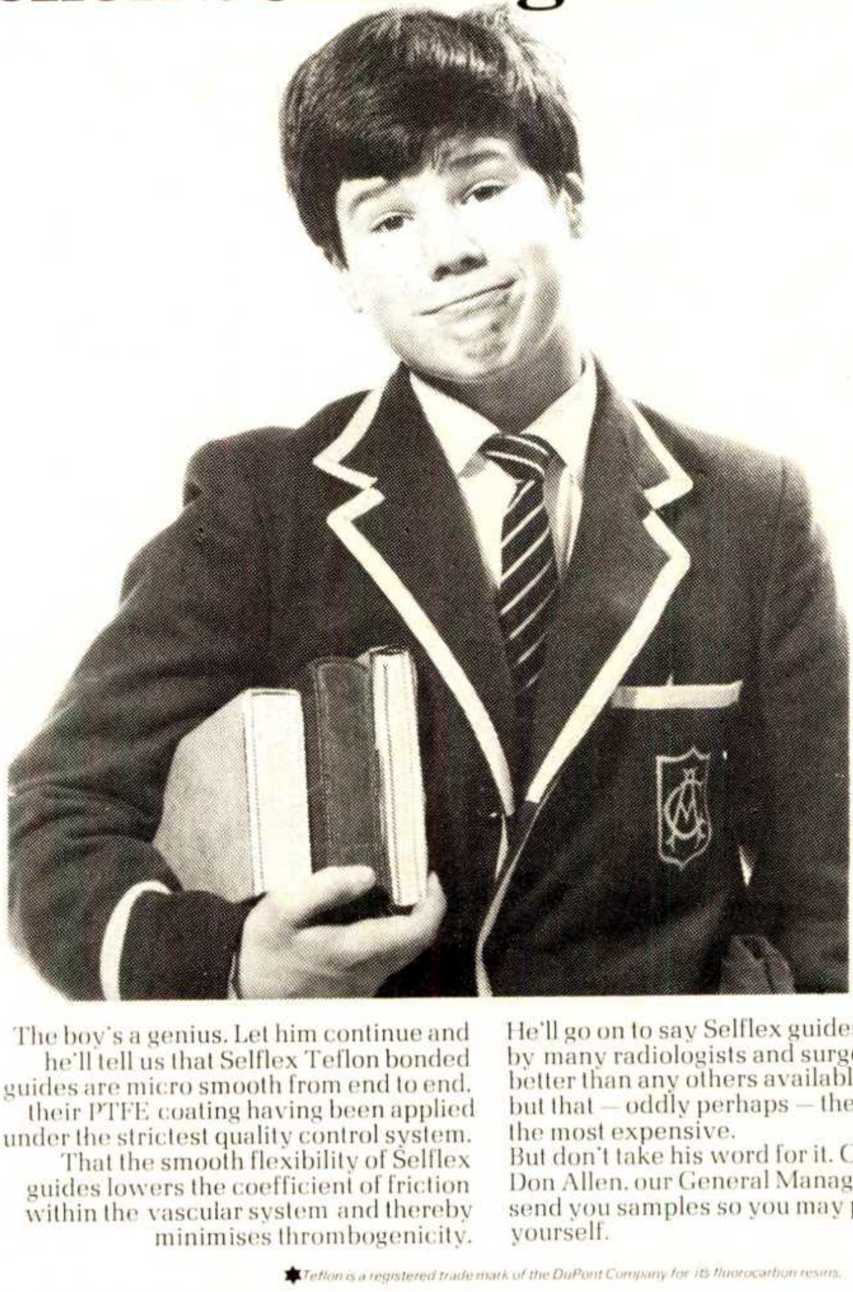

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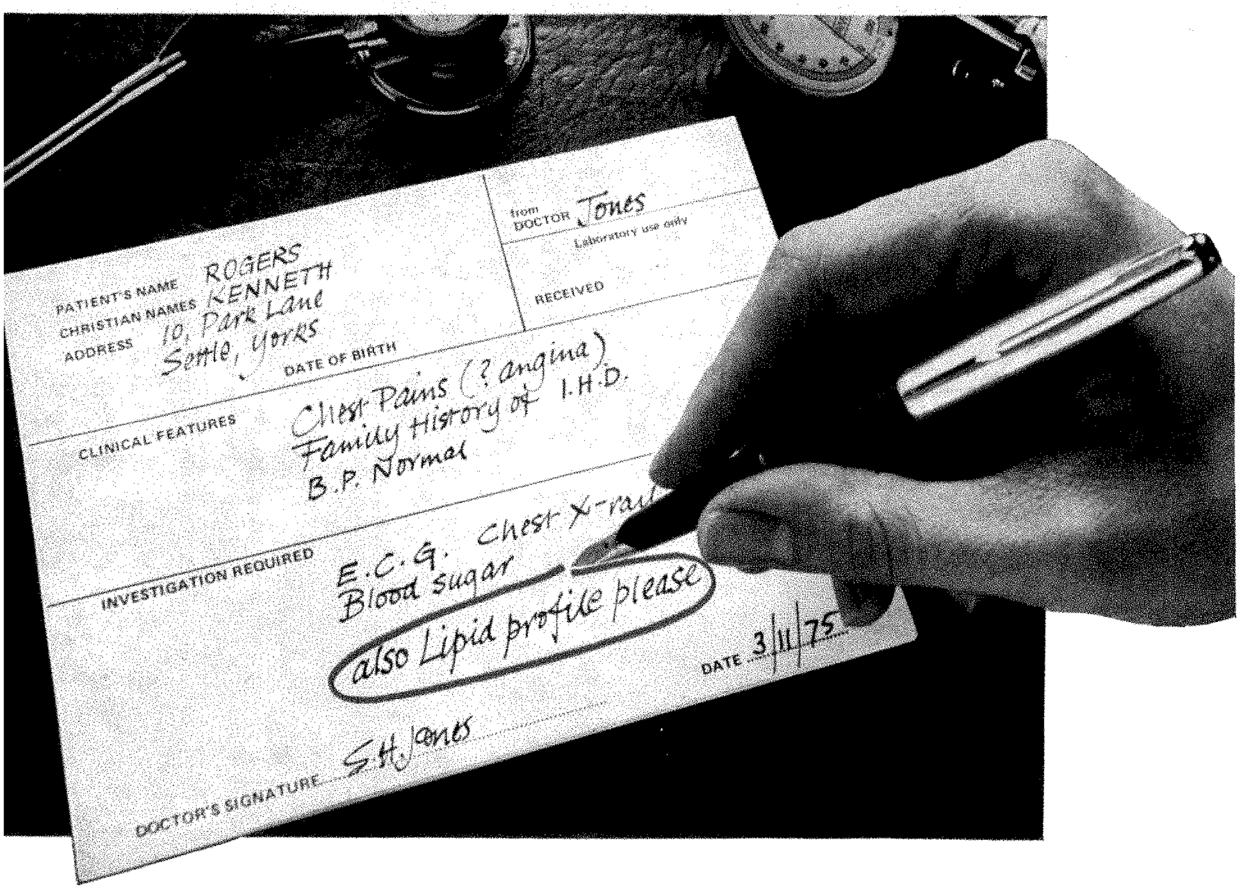

from DOCTOR Jones

Laboratory use only

RECEIVED

PATIENT'S NAME ROGERS

CHRISTIAN NAMES KENNETH

ADDRESS 10, Park Lane
Settle, Yorks

DATE OF BIRTH

CLINICAL FEATURES Chest Pains (? angina)
Family History of I.H.D.
B.P. Normal

INVESTIGATION REQUIRED E.C.G. Chest X-ra
Blood sugar
also Lipid profile please

DATE 3/11/75

DOCTOR'S SIGNATURE S.H. Jones

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REFERENCES
1. Coronary Drug Project Research Group, 1975, *Journal of the American Medical Association* 231, 360.
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# Comparison of 12-lead and computer-analysed 3 orthogonal lead electrocardiogram in coronary artery disease

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*The computer-analysed 3 orthogonal lead system ('3-lead ECG') provides a rapid and consistent interpretation of the electrocardiogram. In 102 patients undergoing selective coronary arteriography, the ability of such a system to predict the presence or absence of coronary artery disease and the site of myocardial ischaemia was compared with that of the conventional scalar electrocardiogram interpreted by cardiologists ('12-lead ECG'). Each system predicted the site of myocardial ischaemia with equal accuracy. The 3-lead ECG was a more sensitive index (3-lead ECG sensitivity=77%; 12-lead ECG sensitivity=70%) but less specific (3-lead ECG specificity=74%; 12-lead ECG specificity=78%). In coronary artery disease, the predictive 'index of merit' for the 3-lead ECG was 0·51, compared with 0·48 for the 12-lead ECG. These results provide further justification for the routine use of the 3 orthogonal lead electrocardiogram.*

The conventional scalar electrocardiogram has for many years proved a useful investigation in the diagnosis of myocardial ischaemia. The limitations of electrocardiography in this field have been stressed (Wood *et al.*, 1950; Doyle *et al.*, 1957; Master and Rosenfeld, 1967; Friesinger and Smith, 1972); approximately 50 per cent of patients with documented coronary atherosclerosis have normal resting electrocardiograms. Despite this, the scalar electrocardiogram remains one of the principal screening procedures in patients presenting with chest pain.

The introduction of selective coronary arteriography has provided a means of establishing the presence or absence of coronary atherosclerosis in the living patient (Kemp *et al.*, 1967; Sones, 1972). Computer-assisted interpretation of the 3 orthogonal lead electrocardiogram has been in operation for some time in this hospital (Macfarlane and Lawrie, 1974) and has removed observer bias and variation in the diagnosis of abnormalities of the electrocardiogram.

It was, therefore, decided to evaluate the usefulness of the computerized electrocardiographic reporting system in the diagnosis of coronary artery disease in patients undergoing selective coronary arteriography.

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## Patients and methods

One hundred and two patients presenting with chest pain warranting selective coronary arteriography were studied. The group consisted of 91 men and 11 women with a mean age of 46·8 years (range 32 to 64 years). Patients with rheumatic heart disease or on digitalis therapy were not included in the study.

Selective coronary arteriography was performed by the technique of Sones or Judkins (Sones and Shirey, 1962; Judkins, 1967). Coronary artery disease was considered to be present when reduction in lumen was greater than 50 per cent in one or more of the three major vessels (right, left anterior descending, and left circumflex coronary arteries). The patients were classified as having a normal vasculature, single, double, or triple vessel disease.

Conventional scalar 12-lead electrocardiograms were recorded using either a Cambridge Transrite 4 or Siemens Cardiostat apparatus. The electrocardiograms thus obtained were reported on independently by two of the authors without knowledge of the result of the coronary arteriogram. Any discrepancies in reporting were settled in committee. The diagnostic criteria for myocardial infarction and myocardial ischaemia were those in common use (Macfarlane, 1970).

Three orthogonal lead electrocardiograms were recorded using the modified axial system (Macfarlane, 1969). Electrocardiograms were tape recorded, using a multichannel FM tape recorder as described previously (Macfarlane *et al.*, 1972), and were replayed to a PDP8E computing system for analysis using the programme which has been reported in detail elsewhere (Macfarlane and Lawrie, 1974). Essentially 8 seconds of leads X, Y, and Z were replayed simultaneously for interpretation and a typical complex was chosen for analysis. Multiple measurements were made by the programme and the interpretation was made on the basis of a check of over 200 criteria. In a previous paper (Cawood *et al.*, 1974) discussing the day-to-day changes in the 3 orthogonal lead electrocardiogram after myocardial infarction, the criteria for the diagnosis of this abnormality were presented. For the detection of ischaemic changes, multiple measurements of the ST-T segment were made. Full details of the criteria used will be published elsewhere (Macfarlane and Lawrie, 1977). In summary the ST-T segment was divided into eight equal time intervals and the amplitude at the end of each was measured. This allowed the detection of ST abnormalities in the early part of the ST-T segment and of terminal T wave abnormalities in the late ST-T segment. In addition, the total negative area of the ST-T segment was measured and compared with normal. The other criterion used for the diagnosis of myocardial ischaemia was an abnormal T vector orientation in either the frontal or transverse plane denoted $T_F$ and $T_T$, respectively. The more important criteria for ischaemic changes can be summarized as follows.

(a) $T_F < 10°$ or $T_T > 70°$.

(b) $T_X < 0{\cdot}05$ mV or $T_Y < 0{\cdot}05$ mV or $T_Z < -0{\cdot}05$ mV.

(c) Depression of the ST onset by 0·02 mV or more, together with a flat or downward sloping ST segment in lead X, Y, or Z.

(d) Inversion of the terminal portion of the T wave in lead X, Y, or Z.

The computer reports thus obtained were reviewed without knowledge of the result of the coronary arteriogram or of the 12-lead electrocardiogram report. Coronary arteriographic assessment of the presence or absence of coronary artery disease was accepted as correct and the sensitivity and specificity (Table 1) of the 3-lead and 12-lead systems were calculated. The 'index of merit' of Hanssen and Kuipers (1965) was adapted to assess the value of each system in predicting the presence or absence of coronary artery disease (Table 2). The site of myocardial ischaemia predicted from the

TABLE 1 *Formulae for sensitivity and specificity*

$$\text{Sensitivity} = \frac{a_1}{a_2} \times 100\%$$

$$\text{Specificity} = \frac{a_3}{a_4} \times 100\%$$

The coronary arteriographic diagnosis is regarded as correct. $a_1$, number with correct ischaemic electrocardiograms; $a_2$, number with coronary artery disease; $a_3$, number with correct normal electrocardiograms; $a_4$, number with normal vessels.

TABLE 2 *Calculation of index of merit (Hanssen and Kuipers, 1965)*

| *Truth* | *Prediction* | |
|---|---|---|
| | *Yes* | *No* |
| Yes | $n_1$ | $n_2$ |
| No | $n_3$ | $n_4$ |

$$\text{Index of merit} = \frac{n_1}{n_1+n_2} + \frac{n_4}{n_3+n_4} - 1$$

$$= \frac{a_1}{a_2} + \frac{a_3}{a_4} - 1 \quad \text{(cf Table 1)}$$

$$= \frac{1}{100}\,(\text{sensitivity}+\text{specificity}) - 1$$

YES and NO refer to presence or absence of coronary artery disease. The coronary arteriogram result is regarded as 'TRUTH'. The number of cases in each category is given by $n_1 \ldots\ldots n_1$. The fraction of correct positives is $\frac{n_1}{n_1+n_2}$, that of correct negatives is $\frac{n_4}{n_3+n_4}$.

TABLE 3 *Expected location of arteriographic occlusion associated with myocardial infarction (James, 1968)*

| *Site of infarct* | *Associated arterial disease* |
|---|---|
| Anteroseptal | LAD |
| Anterior | LAD |
| Anterolateral | $LAD+LC_X$ |
| High lateral | $LC_X$ |
| Inferior | RCA (if right coronary dominant)<br>$LC_X$ (if left coronary dominant) |
| True posterior | RCA (if right coronary dominant)<br>$LC_X$ (if left coronary dominant) |

Abbreviations: LAD=left anterior descending coronary artery. $LC_X$=left circumflex coronary artery. RCA=right coronary artery.

electrocardiogram using each lead system was compared with that predicted from the coronary arteriogram. The expected arterial supply to the various areas of the left ventricular myocardium is summarized in Table 3 (James, 1968).

## Results

Twenty-five patients had a normal coronary vasculature on selective coronary arteriography, while 77 patients (75%) were shown to have significant lesions affecting one or more vessels. Of those with coronary artery disease, 13 patients had single vessel disease, 29 double vessel disease, and 35 triple vessel disease. The distribution of affected vessels is shown in Table 4.

TABLE 4 *Distribution of coronary artery disease in 77 patients*

| *Coronary arteriogram* | *Vessel affected* | *No of patients* |
|---|---|---|
| Single vessel disease (13) | RCA | 4 |
| | LAD | 9 |
| | $LC_x$ | — |
| Double vessel disease (29) | RCA+LAD | 20 |
| | $RCA+LC_x$ | 4 |
| | $LAD+LC_x$ | 5 |
| Triple vessel disease (35) | $RCA+LAD+LC_x$ | 35 |

Abbreviations as for Table 3.
Number in brackets equals total number of patients in each group.

TABLE 5 *12-lead electrocardiogram report related to the coronary arteriogram in 92 patients**

| *Coronary arteriogram* | *Normal electrocardiogram* | *Ischaemic electrocardiogram* |
|---|---|---|
| Normal (23) | 18 (78%) | 5 |
| Single vessel disease (11) | 5 | 6 (54%) |
| Double vessel disease (27) | 10 | 17 (63%) |
| Triple vessel disease (31) | 6 | 25 (81%) |
| Coronary artery disease Total (69) | 21 | 48 (70%) |

*Excluding those with left ventricular hypertrophy or left bundle-branch block on 12-lead electrocardiogram.

TABLE 6 *'Ischaemic' electrocardiogram (12-lead system) related to the coronary arteriogram**

| *Coronary arteriogram* | *'Ischaemic' electrocardiogram* | |
|---|---|---|
| | *Myocardial infarction* | *ST-T changes* |
| Single vessel disease | 3 | 3 |
| Double vessel disease | 11 | 6 |
| Triple vessel disease | 13 | 12 |

*Excluding those with left ventricular hypertrophy or left bundle-branch block on 12-lead electrocardiogram.

### 12-lead electrocardiogram

Four electrocardiographic categories were encountered in this study: (i) normal tracing, (ii) 'myocardial ischaemia', either with evidence of a transmural infarct, or with ischaemic repolarization abnormalities, (iii) left ventricular hypertrophy (LVH), and (iv) left bundle-branch block (LBBB). The latter two diagnoses (LVH and LBBB) were present in 8 and 2 patients, respectively. Of those with LVH, 2 patients were hypertensive (BP > 140/90 mmHg (18·6/12·0 kPa)); the remainder were normotensive at the time of study. Excluding these two categories, the 12-lead electrocardiogram was normal in 18 out of 23 patients with normal vessels (Table 5). Five patients with normal vessels had 'ischaemic' electrocardiograms, the changes being restricted to repolarization abnormalities (specificity =78%).

The resting 12-lead electrocardiogram was ischaemic in 48 out of 69 patients with coronary artery disease (sensitivity=70%). The electrocardiographic criteria for myocardial ischaemia were satisfied more frequently as the extent of coronary artery disease increased (Table 5). The criteria for myocardial infarction were fulfilled in 27 of the 48 'ischaemic' electrocardiograms (56%). The frequency with which electrocardiographic evidence of transmural infarction occurred did not correlate with the extent of disease (Table 6). In all instances of myocardial infarction, the site of ischaemia predicted from the 12-lead electrocardiogram agreed with that predicted from the coronary arteriogram.

The 'index of merit' of the 12-lead system in predicting the presence or absence of coronary artery disease was 0·47.

TABLE 7 *3-lead electrocardiogram report related to the coronary arteriogram in 89 patients**

| *Coronary arteriogram* | *Normal electrocardiogram* | *'Ischaemic' electrocardiogram* |
|---|---|---|
| Normal (23) | 17 (74%) | 6 |
| Single vessel disease (11) | 4 | 7 (64%) |
| Double vessel disease (25) | 6 | 19 (76%) |
| Triple vessel disease (30) | 5 | 25 (83%) |
| Coronary artery disease Total (66) | 15 | 51 (77%) |

*Excluding those with left ventricular hypertrophy or left bundle-branch block on 3-lead electrocardiogram.

### 3-lead electrocardiogram

Computer-assisted orthogonal 3-lead electrocardiogram reports also fell into the same four categories (normal, 'myocardial ischaemia', left ventricular hypertrophy, and left bundle-branch block). The latter two diagnoses were made in 11 and 2 patients, respectively. Of those with left ventricular hypertrophy, 2 patients were hypertensive (BP > 140/90 mmHg (18·6/12·0 kPa)); the other 9 were normotensive at the time of study. Excluding these two diagnoses, the resting 3-lead electrocardiogram was normal in 17 out of 23 patients with normal vessels (specificity = 74%). In 5 patients repolarization abnormalities were reported and in one patient an inferior myocardial infarction was diagnosed.

The 3-lead electrocardiogram diagnosed 'myocardial ischaemia' in 51 of 66 patients with coronary artery disease (sensitivity = 77%) (Table 7). The diagnosis was made with increasing frequency with increasing extent of coronary artery disease. Transmural myocardial infarction was reported in 25 (49%) of the patients with 'ischaemic' electrocardiograms (Table 8). Again, no correlation was apparent between the frequency with which myocardial infarction was diagnosed and the extent of disease. As with the 12-lead system, the predicted site of ischaemia agreed with that predicted from the coronary arteriogram in all cases of myocardial infarction.

The 'index of merit' for the 3-lead system in predicting the presence or absence of coronary artery disease was 0·51.

TABLE 8 *'Ischaemic' electrocardiogram (3-lead system) related to the coronary arteriogram**

| *Coronary arteriogram* | *'Ischaemic' electrocardiogram* | |
|---|---|---|
| | *Myocardial Infarction* | *ST-T changes* |
| Single vessel disease | 3 | 4 |
| Double vessel disease | 9 | 10 |
| Triple vessel disease | 13 | 12 |

*Excluding those with left ventricular hypertrophy or left bundle-branch block on 3-lead electrocardiogram.

### Comparison of reports

In 88 patients (86%), the 12-lead and 3-lead electrocardiogram reports were identical. The discordant reports are listed in Table 9. In 6 patients with proven coronary artery disease (8%) the 3-lead electrocardiogram diagnosed 'myocardial ischaemia' not reported by the 12-lead system. However, in 4 patients with proven coronary artery disease and 'ischaemic' 12-lead electrocardiograms, the 3-lead system reported left ventricular hypertrophy with accompanying ST and T wave abnormalities. The reverse was reported in one patient. In all, left ventricular hypertrophy was diagnosed in 12 patients, 11 by the 3-lead and 8 by the 12-lead system. One patient had normal vessels, but the remainder had coronary artery disease. Left ventricular hypertrophy was reported, therefore, by the 3-lead system in 13 per cent of patients with coronary artery disease and by the 12-lead system in 9 per cent. Two of these patients were hypertensive (BP > 140/90 mmHg (18·6/12·0 kPa)); the remainder were normotensive (mean BP 131/76 mmHg (17·4/10·1 kPa)).

## Discussion

The number of 'ischaemic' electrocardiograms in both systems is higher than reported by certain

TABLE 9 *Discordant 3-lead and 12-lead electrocardiogram reports in 14 patients*

| *Coronary arteriogram* | *12-lead report* | *3-lead report* |
|---|---|---|
| Normal | Normal | Inferior ischaemia |
| | Inferolateral ischaemia | Inferior infarction |
| Single vessel disease | | |
| LAD | Normal | Anterolateral ischaemia |
| Double vessel disease | | |
| RCA+LAD | Normal | Inferior ischaemia |
| RCA+LAD | Normal | Anterolateral ischaemia |
| RCA+LAD | Anteroseptal infarction | Left ventricular hypertrophy |
| RCA+LAD | Normal | Inferolateral ischaemia |
| RCA+ LAD | Inferior ischaemia | Left ventricular hypertrophy |
| RCA+LC$_x$ | Normal | True posterior infarction |
| Triple vessel disease | | |
| (RCA+LAD+LC$_x$) | Lateral ischaemia | Left ventricular hypertrophy |
| | Anterolateral infarction | Anterolateral ischaemia |
| | Normal | Subepicardial ischaemia |
| | Left ventricular hypertrophy | Anterolateral ischaemia |
| | Anterolateral ischaemia | Left ventricular hypertrophy |

authors (Wood *et al.*, 1950; Doyle *et al.*, 1957; Master and Rosenfeld, 1967; Hultgren *et al.*, 1967; Friesinger and Smith, 1972) in patients suspected of having coronary atherosclerosis. Others have reported a similar proportion of abnormal electrocardiograms in patients with clinical ischaemic heart disease and unequivocal coronary artery disease (Elliott and Gorlin, 1966). This discrepancy may be explained by patient selection since, in this study, the majority of patients were drawn from a second referral clinic, often presenting with typical cardiac ischaemic pain. Such a group does not, therefore, represent a true cross-section of the coronary atherosclerosis population.

The 3 orthogonal lead electrocardiogram reporting system described has been shown to predict more accurately the presence or absence of coronary artery disease subsequently proven by selective coronary arteriography (index of merit for 3-lead system=0·51, and for 12-lead system=0·48). It is not feasible to test for a statistically significant difference between these two indices. It is possible to show that there is no statistically significant difference between corresponding components of the index of merit, viz. the fractions of correct positives and correct negatives (Table 2), obtained from 3-lead and 12-lead electrocardiograms. It should be noted, however, that this index is designed to show up differences between diagnostic methods on a scale of 0 to 1. If the sensitivity is 100 per cent and specificity is 0 per cent, then the index of merit is 0; likewise if both sensitivity and specificity are 50 per cent then the index of merit is also 0. If both sensitivity and specificity are ideal at 100 per cent then the index of merit has the optimal value of 1. Thus, the higher the index of merit, the better the technique.

The 3-lead electrocardiogram was a more sensitive index of the presence of coronary artery disease but slightly less specific compared with the 12-lead electrocardiogram. With both systems, the predicted site of myocardial infarction correlated closely with the area of ischaemia predicted from the coronary arteriogram. False positive reports (i.e. 'ischaemic' electrocardiograms in patients with normal coronary vessels) were common with both 3-lead and 12-lead systems. The ischaemic abnormalities encountered were restricted in all but one patient to repolarization changes. The high frequency of 'ischaemic' electrocardiograms in the normal vessel group is not really surprising. The population studied, as discussed above, could scarcely be considered normal since none was asymptomatic. In addition, the paradox of angina pectoris in the presence of normal coronary vessels is well established (Kemp *et al.*, 1973; James, 1970; Waxler, Kimbris, and Dreifus, 1971; Eliot and Bratt, 1969; Likoff, Segal, and Kasparian, 1967). Many of these patients have objective evidence of myocardial ischaemia, either on the electrocardiogram or on exercise testing or atrial pacing with coronary sinus lactate sampling (Dwyer, Wiener, and Cox, 1969; Bemiller, Pepine, and Rogers, 1973; Arbogast and Bourassa, 1973; Helfant *et al.*, 1970; Boudoulas *et al.*, 1974).

Left ventricular hypertrophy was a fairly common electrocardiographic diagnosis in the patients with coronary artery disease (3-lead system 13%; 12-lead system 9%). Left ventricular hypertrophy in coronary artery disease (in the absence of hypertension) has been reported in necropsy studies (Ellis *et al.*, 1962; McCain, Klein, and Gilson, 1950; Murata *et al.*, 1972) while haemodynamic and angiographic studies *in vivo* have shown increased left ventricular mass in patients with coronary artery disease compared with those with normal coronary arteriograms (Pech *et al.*, 1974). Hence, in the absence of a recognized predisposing factor to left ventricular hypertrophy, such an abnormality may well be a further index of myocardial ischaemia. If this were accepted, the sensitivity of the 3-lead electrocardiogram in diagnosing coronary artery disease would rise to 80 per cent and of the 12-lead to 72 per cent, altering the specificity to 71 per cent for the 3-lead and 75 per cent for the 12-lead electrocardiogram.

In a recent paper, Talbot *et al.* (1973) argued that the 3-lead and 12-lead systems of recording were complementary and that all 15 leads were 'essential' for computer-assisted electrocardiographic interpretation. Our own opinion is that the diagnostic gain in adopting such an approach is negligible when adequate criteria for the 3-lead electrocardiogram are chosen. Furthermore, the increase in computer time to undertake adequate wave recognition procedures on 15 leads so prolongs the analysis that it could become uneconomic. In this particular study, 86 per cent of patients had identical reports. The use of 12 conventional leads as well as the 3 orthogonal leads would have led to 4 (4%) additional reports of myocardial ischaemia or infarction. In each case, however, ST-T abnormalities were already detected by the computer-analysed electrocardiogram but placed in the diagnostic category of left ventricular hypertrophy. Conversely the use of 3 orthogonal leads in addition to the 12 conventional leads would have led to a further 5 (5%) reports of myocardial ischaemia or infarction in patients with single, double, or triple vessel disease who had normal 12-lead electrocardiograms.

In summary, the 3-lead electrocardiogram has been shown to have an enhanced 'index of merit' for the prediction of the presence or absence of coronary artery disease and has an equal ability to indicate the site of myocardial ischaemia compared with the 12-lead electrocardiogram. The technique is more sensitive than the 12-lead electrocardiogram but at the expense of slight lessening of specificity. This favourable performance provides further justification for the routine use of 3 orthogonal lead electrocardiography.

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# Orthogonal electrocardiogram, apex cardiogram, and atrial sound in normotensive and hypertensive 50-year-old men

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*The prevalence of signs of heart involvement was studied non-invasively in a group of untreated hypertensives ($n=35$) and a reference group ($n=73$), all derived from a random population sample of 50-year-old men. Signs of left ventricular hypertrophy were studied by means of orthogonal electrocardiography and conventional electrocardiography. Signs of decreased distensibility of the left ventricle were studied by apex cardiography and registration of atrial sounds.*

*Left ventricular hypertrophy among hypertensives was significantly more common according to orthogonal electrocardiography (33%) than according to conventional electrocardiography (9%), indicating that the former may be a better method for detection of left ventricular hypertrophy than the latter. In the hypertension group the amplitude of the R wave in lead X on orthogonal electrocardiography was positively correlated to casual diastolic blood pressure ($r=0{\cdot}40$) and to diastolic blood pressure after one hour's rest ($r=0{\cdot}65$). The degree of pressure load leading to left ventricular hypertrophy seems to be better reflected by resting than by casual blood pressure.*

*There was no hypertensive subject with both signs of left ventricular hypertrophy on orthogonal electrocardiography and either an a/H ratio over 15 per cent or an abnormal atrial sound, indicating two different forms of cardiac involvement as the result of hypertension. Casual blood pressures became normal during rest in hypertensives with a/H ratio over 15 per cent on apex cardiography or abnormal atrial sound, but not in hypertensives with signs of left ventricular hypertrophy on orthogonal electrocardiography.*

The natural history of hypertension is extremely varied. One-third of a hypertensive population survived to old age without signs of organic damage while in others the prognosis was poor (Fry, 1974). Hypertensives with signs of left ventricular hypertrophy on electrocardiography have a poorer prognosis than hypertensives with a normal electrocardiogram (Bechgaard, 1967; Sokolow and Perloff, 1961; Kannel *et al.,* 1970). In mild to moderate hypertension, antihypertensive treatment had a beneficial effect in hypertensives with signs of cardiac abnormality on electrocardiography or *x*-ray, while no benefit could be shown in hypertensives without such abnormality (Veterans Administration Co-operative Study Group on Antihypertensive Agents, 1972). Thus, it seems important for prognostic and therapeutic purposes to diagnose cardiac abnormality in hypertensives. Conventional electrocardiography and chest *x*-ray are, however, normal in many hypertensives, partly because of low sensitivity, and are less suitable for quantification of left ventricular hypertrophy (Sokolow and Lyon, 1949; Gamboa, Hugenholtz, and Nadas, 1965; The National Center for Health Statistics, 1966; Tibblin, 1967, Romhilt and Estes, 1968; Sannerstedt, Bjure, and Varnauskas, 1970; McCaughan, Littman, and Pipberger, 1973).

Vectorcardiography and orthogonal electrocardiography have been shown to be superior to conventional electrocardiography in the diagnosis of left ventricular hypertrophy (Gamboa *et al.,* 1965; McCaughan *et al.,* 1973). Apex cardiography, especially the *a* wave in the apex cardiogram, and the analogous acoustical event, the atrial sound, provide non-invasive ways of assessing changes in

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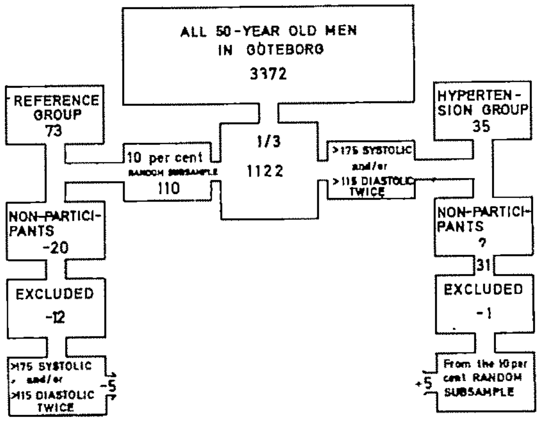

FIG. 1 *Schematic representation of the random selection of the hypertension group and the reference group from the population of men born in 1921 and living in Göteborg, Sweden.*

left ventricular distensibility (Bethell and Nixon, 1973; Gibson *et al.*, 1974; Tavel, 1974). In the present investigation signs of left ventricular hypertrophy were studied by conventional and orthogonal electrocardiography (Frank), and signs of decreased left ventricular distensibility by apex cardiography and registration of atrial sounds phonocardiographically.

The aim of the present study was to determine the prevalence of heart involvement, assessed by these non-invasive methods, in groups of untreated hypertensive and normotensive men, homogeneous with respect to age, and to relate the findings to casual blood pressure and resting blood pressure.

## Subjects

From a screening examination, which was part of a multifactorial, primary preventive trial (Wilhelmsen, Tibblin, and Werkö, 1972) in a randomly selected third (n=1122) of the 50-year-old male population in Göteborg, Sweden, all subjects with untreated, essential hypertension were allocated to a hypertension group (n=35) (see Fig. 1). The diagnosis of essential hypertension was based on a casual blood pressure above 175 mmHg (23·3 kPa) systolic and/or 115 mmHg (15·3 kPa) diastolic on two separate occasions two weeks apart (the casual blood pressure values given in the tables refer to the first measurement), and a negative standard diagnostic examination for secondary hypertension (Wilhelmsen, Berglund, and Werkö, 1973). Thus, one subject with chronic glomerulonephritis was excluded (Fig. 1). For the hypertension group, 18 subjects were classified as belonging to WHO stage 1, 13 to stage 2, and 4 to stage 3.

A reference group (n=73) was obtained from the same trial by drawing a 10 per cent subsample at random. The non-participation rate in the subsample was 18 per cent (20/110). Five subjects in the reference group fulfilled the criteria for hypertension and joined the hypertension group. Twelve subjects in the reference group were excluded, 1 with mitral stenosis, 1 with aortic regurgitation, 5 who were on antihypertensive treatment, and 5 with casual blood pressure above 175 mmHg (23·3 kPa) systolic and/or 115 mmHg (15·3 kPa) diastolic at screening but not at the subsequent blood pressure control two weeks later. No subject in the hypertension group had a history of valvular heart disease.

In addition to the above-mentioned groups, 3 untreated, male hypertensives (aged 45, 50, and 50 years) with casual blood pressures above 240 mmHg (31·9 kPa) systolic and 160 mmHg (21·3 kPa) diastolic, recruited from the same screening examination, were examined in order to obtain data from subjects with extremely high blood pressures. These 3 subjects all belonged to WHO stage 3.

Orthogonal electrocardiograms and conventional electrocardiograms were recorded in all subjects (n=111). Registration of apex cardiogram, atrial sounds, and resting blood pressure were performed in a randomly selected half of both the reference (n=36) and the hypertension group (n=19) and in the 3 hypertensives with extremely high blood pressure. Analysis of each variable was performed without knowledge of the results of the other examinations or to which group the subject belonged. Resting blood pressure values were, for technical reasons, lacking for 4 subjects selected for apex cardiography; all 4 belonged to the reference group. At analysis of signs of left ventricular hypertrophy on electrocardiography, 2 subjects in the hypertension group and 1 in the reference group with left or right bundle-branch block or left anterior hemiblock, were excluded, since changes in left ventricular activation have an influence on the amplitudes (Fernandez, Scabat, and Lenegre, 1970). In 4 subjects in the reference group (11%) and 1 hypertensive subject (5%), an acceptable apex cardiogram could not be recorded.

## Methods

Conventional electrocardiograms, apex cardiograms, phonocardiograms, and resting blood pressures were all registered on a direct writing ink-jet 7-channel mingograph (EM 81, Siemens-Elema, Sweden) with and linear frequency response from 0 to 500 Hz 30 per cent amplitude reduction at 650 Hz. The mingograph was supplied with a phonopreamplifier (EMT 22) with electrical filters that together with a piezoelectric microphone (EMT 25 C) give five frequency ranges with the following nominal frequencies: 25, 50, 100, 200, 400 Hz and one aural frequency range. A crystal transducer (EMT 510 C) with low frequency time constant between 1·9 and 4·6 s (depending on a capacitance—resistance product, decided by the individual amplification used for each curve) connected by a 35 to 40 cm long rubber tube to a specially designed capillary damped funnel pick-up, 2·5 cm in diameter, giving a frequency response of 0·08 (at time constant 1·9 s) to 65 Hz (–3db), was used. Paper speed was 50 mm/s for electrocardiogram and for the other tracings 100 mm/s.

Blood pressure was measured with a 12 cm broad and 26 cm long rubber cuff. Cuff inflation was rapid, cuff deflation approximately 3 beats per 10 mmHg (1·3 kPa). Diastolic pressure was registered as phase 5, i.e. when the sounds disappeared. Casual blood pressure was measured in the seated position with a mercury manometer and stethoscope at the screening examination. Resting blood pressure was measured after one hour's rest in the supine position in a sound-protected room with an automatic device for cuff inflation and deflation (Boucke-Brecht), with a microphone (EMT 25 C) placed over the right brachial artery and with simultaneous registration of cuff pressure, Korotkoff sounds, and electrocardiogram. The largest circumference of the relaxed right overarm was measured in those subjects in whom resting blood pressure was measured.

Casual heart rate was measured as the mean of five consecutive beats from an electrocardiogram taken at the screening examination. Resting heart rate was measured from the resting blood pressure recordings. The resting blood pressure was measured twice with an interval of one minute. The following correlations between these resting blood pressures were found: reference group systolic $r=0{\cdot}95$, diastolic $r=0{\cdot}94$; hypertension group systolic $r=0{\cdot}94$, diastolic $r=0{\cdot}96$. No significant correlation for the relation between the circumference of the right upper arm and resting blood pressure was found (reference group $r=0{\cdot}11$ systolic, $r=0{\cdot}17$ diastolic; hypertension group $r=0{\cdot}09$ systolic, $r=0{\cdot}31$ diastolic). There was no significant difference in the mean of the right upper arm circumference between the hypertension group ($\bar{x}$ 31·8, $s_x$ 2·5, range 27·0 to 35·5 cm) and the reference group ($\bar{x}$ 30·8, $s_x$ 2·1, range 26·0 to 35·5 cm).

The three scalar electrocardiographic leads X, Y, and Z were simultaneously recorded on magnetic tape (Hellige) using the Frank's corrected orthogonal lead system (Frank, 1956). Computer analysis was performed according to Arvedson (1968, 1973) with a sampling frequency of 200 per second. The following criteria for left ventricular hypertrophy were used: the amplitude of the R wave in lead X ($R_x$) above 1·8 mV, the R wave in lead X and the S wave in lead Y ($R_x+S_y$) above 1·9 mV or the R wave in lead Z ($R_z$) above 1·3mV. Since most electrocardiographic measurements are not normally distributed the amplitude limits were drawn at the upper 97·5th centile in the reference group in analogy with a previous study (McCaughan *et al.*, 1973). The upper 97·5th centile in the reference group was also studied for $R_x+R_z$ (2·8 mV), the spatial maximal amplitude (2·2 mV), ventricular activation time (0·06 s for both $R_x$ and the spatial maximal amplitude), the duration of the P wave (0·13 s) and the following amplitudes of the P wave in the orthogonal electrocardiogram: sum of positive P amplitudes in lead X and lead Z (0·17 mV), positive P amplitude in lead Z (0·07 mV) (Ishikawa, Kini, and Pipberger, 1973). Conventional electrocardiograms were recorded as standard 12 lead electrocardiograms using the right arm as the indifferent electrode for the praecordial leads. Electrocardiograms were coded in accordance with the Minnesota code (Blackburn *et al.*, 1960). Amplitude measurements in praecordial leads were done in accordance with the revision for CR leads (Åstrand *et al.*, 1967). As signs of left ventricular hypertrophy, a combination of amplitude criteria, 3:1 or 3:3, and ST or T criteria, 4:1–3 or 5:1–3, were used (Sokolow and Lyon, 1949).

Apex cardiograms and phonocardiograms were recorded during the resting period preceding the measurement of resting blood pressure. The apex cardiogram was recorded simultaneously with electrocardiogram lead II and a phonocardiogram from the third left intercostal space parasternally with the subject in the left lateral position during relaxed expiratory apnoea. The pick-up was held by hand at the point of maximal impulse of the apex beat. The *a* wave percentage amplitude of the total deflection of the apex cardiogram (H), was calculated as the mean of five consecutive beats (Fig. 2). An *a*/H ratio above 15 per cent was considered abnormal (Tavel *et al.*, 1965; Epstein *et al.*, 1968; Voigt and Friesinger, 1970). Registration of the apex cardiogram by two different examiners with one hour's interval, the second examiner not being allowed to see the recording made by the first examiner, gave a correlation coefficient of 0·88 ($n=81$) between the two calculated *a*/H

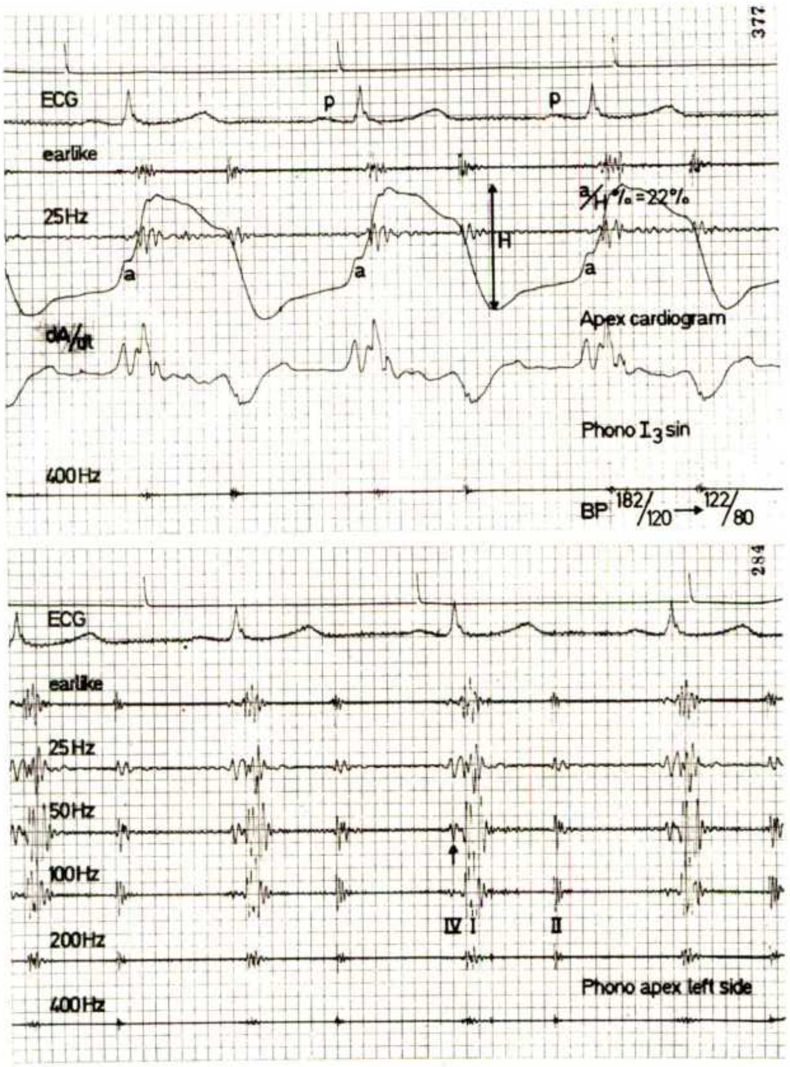

FIG. 2 *Apex cardiogram and phonocardiogram in a hypertensive subject in the left lateral position. Upper panel: apex cardiogram with an abnormal a wave (a). The a wave percentage amplitude of the total deflection of the apex cardiogram (H) was 22 per cent calculated as the mean a/H ratio of 5 consecutive beats. The apex cardiogram was recorded simultaneously with electrocardiogram lead II, phonocardiogram from the third intercostal space parasternally, and the first derivative of the apex cardiogram (dA/dt). Screening blood pressure (BP) was 182/120 mmHg (24·2/16·0 kPa), resting blood pressure was 122/80 mmHg (16·2/10·6 kPa). Lower panel: phonocardiogram from the apex region showing an atrial sound of intensity 4. The phonocardiogram was recorded with six frequency ranges giving five nominal frequencies from 25 to 400 Hz and one aural frequency range.*

ratios, with a standard deviation of a single determination of 2·5 per cent.

Phonocardiograms were recorded during relaxed expiratory apnoea simultaneously with electrocardiographic lead II from the routine clinical auscultation points including registration over the apex in the left lateral position (Fig. 2). One of the authors (I.W.) with long experience of phonocardiography, classified the atrial sound in the phonocardiogram with regard to its intensity, on a five-point subjective scale, where 1 was judged as 'very weak' and 5 as 'very strong'. Atrial sounds of intensity 4 and 5 were arbitrarily classified as abnormal. A blind re-evaluation of the phonocardiograms with respect to the intensity of the atrial sound was performed after one year. One atrial sound in the hypertension group that had previously been evaluated as 4 was now judged to be 3. This subject had an abnormal a wave in the apex cardiogram. At the latter evaluation the proportion of subjects with abnormal atrial sounds was not significantly higher in the hypertension group than in the reference group.

An abnormal atrial sound is said to have the same haemodynamic significance as an abnormal *a* wave in the apex cardiogram (Tavel, 1974; Bethell and Nixon, 1973). Good correlation has been shown between the relative magnitude of the *a* wave and an index of the left ventricular distensibility (Gibson *et al.*, 1974). Therefore, an abnormal *a* wave in the apex cardiogram and an abnormal atrial sound were both regarded as signs of decreased left ventricular distensibility.

Standard methods were used for calculation of the mean ($\bar{x}$), the standard deviation ($s_x$), the standard error of the mean ($s_{\bar{x}}$), and the linear correlation coefficient (r). The hypothesis of no differences in means was tested with Student's t-test or the Wilcoxon Rank Sum Test for two samples. The hypothesis of no differences between paired observations in the same subjects was tested with Student's t-test for paired observations. Where the standard deviation and range are given the t-test was used; where the standard error of the mean and range are given the Wilcoxon test was used. The hypothesis of no differences in proportions between two groups was tested with the Fisher exact test for $n < 60$ and with the $\chi^2$ test for $n \geq 60$. The hypothesis of no differences in proportions when examining one group of subjects with two separate methods was tested with McNemar's test for correlated proportions (Remington and Schork, 1970). The formula $\sqrt{\frac{\Sigma d_i^2}{2n}}$ was used to calculate the standard deviation of a single determination in a series of determinations of which the mean difference was not significant (Dahlberg, 1940). Only two-tailed tests were used and differences were considered significant for P values 0·05 or less.

## Results

### Blood pressure and heart rate

In both the hypertension and the reference group the resting systolic and diastolic blood pressures and heart rates were significantly lower ($P < 0{\cdot}001$) than the casual (Table 1). The hypertensives showed significantly higher ($P < 0{\cdot}05$) casual heart rate than the reference group, but after one hour's rest in a sound-protected room there was no significant difference. The differences in resting systolic and diastolic blood pressure between the two groups were significant ($P < 0{\cdot}001$).

TABLE 1 *Casual and resting blood pressure and heart rate in subjects randomly selected for apex cardiography*

| | | | *Hypertension group No.=19* | | | *Reference group No.=32* | | |
|---|---|---|---|---|---|---|---|---|
| | | | $\bar{x}$ | *Range* | $s_x$ | $\bar{x}$ | *Range* | $s_x$ |
| Systolic | Casual | mmHg | 197 | (220–164) | 15 | 142 | (174–116) | 15 |
| | Resting | | 154 | (192–111) | 23 | 123 | (152–104) | 13 |
| Diastolic | Casual | mmHg | 119 | (138–98) | 9 | 92 | (110–70) | 8 |
| | Resting | | 96 | (120–64) | 15 | 77 | (96–51) | 10 |
| Heart rate | Casual | beats/min | 84 | (114–61) | 17 | 75 | (114–54) | 15 |
| | Resting | | 61 | (74–43) | 8 | 60 | (83–46) | 8 |

*Conversion factor from Traditional to SI Units:* 1 mmHg≈0 133 kPa.

TABLE 2 *Selected scalar measurements on orthogonal and conventional electrocardiography that discriminate between hypertension and reference groups*

| | *Hypertension group* No. | % | *Reference group* No. | % |
|---|---|---|---|---|
| Orthogonal electrocardiogram | | | | |
| $R_x > 1\ 8$ or $R_z > 1\ 3$ or $R_x + S_y > 1\ 9$ mV | 11/33 | 33 | 2/72 | 3 |
| Conventional electrocardiogram | | | | |
| 3:1 or 3:3 plus 4:1–3 or 5:1–3 | 3/33 | 9 | 2/72 | 3 |
| 3:1 or 3:3 alone | 6/33 | 18 | 5/72 | 7 |

## Orthogonal electrocardiogram and standard 12-lead electrocardiogram

The proportion of hypertensives with signs of left ventricular hypertrophy on orthogonal electrocardiogram (11/33, 33%) was significantly higher ($P < 0{\cdot}001$) than that in the reference group (2/72, 3%), see Table 2. The proportion of hypertensives with signs of left ventricular hypertrophy with conventional electrocardiogram was 9 per cent (3/33), compared with 3 per cent (2/72) in the reference group Minnesota code 3:1 or 3:3 alone was seen in 18 per cent (6/33) of the hypertensives and in 7 per cent (5/72) of the reference group. The proportion of hypertensives with signs of left ventricular hypertrophy by orthogonal electrocardiogram was significantly higher (McNemar, $P < 0{\cdot}025$) than by conventional electrocardiogram. In the reference group there was no overlapping between the two methods, i.e. two subjects showed signs of left ventricular hypertrophy by orthogonal electrocardiogram, and another two by conventional electrocardiogram. Of the hypertensives, one fulfilled the criteria for left ventricular hypertrophy with conventional electrocardiogram only, two with both methods, and nine with orthogonal electrocardiogram only. Of these nine subjects, none had a Minnesota code 4:1–3 or 5:1–3, i.e. ST or T changes on conventional electrocardiogram, and thus the only sign of left ventricular hypertrophy in these nine hypertensives was high QRS amplitude on orthogonal electrocardiogram. Other measurements, such as $R_x + R_z$, the spatial maximal amplitude, ventricular activation time, or the duration or amplitude of the P wave did not improve the discrimination between the hypertension and reference group.

## Apex cardiogram and atrial sound

The proportion of hypertensives with *a*/H ratio above 15 per cent (7/18, 39%) was significantly higher ($P < 0{\cdot}05$) than found in the reference group (2/32, 6%), see Fig 3. The mean *a*/H ratio in the hypertension group ($\bar{x} = 13{\cdot}9$, $s_{\bar{x}} = 1{\cdot}3$, range 6 to 28) was significantly higher ($P < 0{\cdot}01$) than the mean in the reference group ($\bar{x} = 9{\cdot}9\%$, $s_{\bar{x}} = 1{\cdot}0$, range 0 to 33).

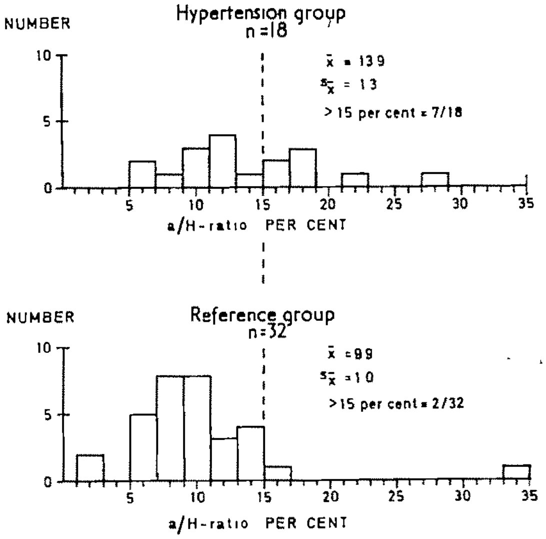

FIG. 3 *Distribution of the a/H ratio from the apex cardiogram and the proportion of subjects with a/H ratio above 15 per cent, the mean ($\bar{x}$) and the standard error of the mean ($s_{\bar{x}}$) in the hypertension and reference group. For practical reasons, one subject in the reference group with a/H ratio=0 per cent was placed in the interval 1 to 3 per cent in the figure.*

Atrial sounds of intensity 1 to 3 were common in both groups (Fig. 4). The proportion of hypertensives with atrial sounds of intensity 4 and 5 (5/19, 26%) was significantly higher ($P < 0{\cdot}05$) than in the reference group (1/36, 3%). All abnormal atrial sounds had their maximum intensity over the apex in the left lateral position. No measurements of the atrial sound percentage amplitude of the first heart sound could discriminate between the groups. Three of the seven hypertensives who had a *a*/H ratio above 15 per cent also had abnormal atrial sounds. One of the two subjects in the reference group, who had an abnormal *a* wave on the apex cardiogram, had diabetes mellitus and a high casual blood pressure (172/98 mmHg (22·9/13·0 kPa)). The other subject with *a*/H ratio 33 per cent had angina pectoris. He also had an abnormal atrial sound (intensity 5) and ST and T changes on conventional electrocardiography.

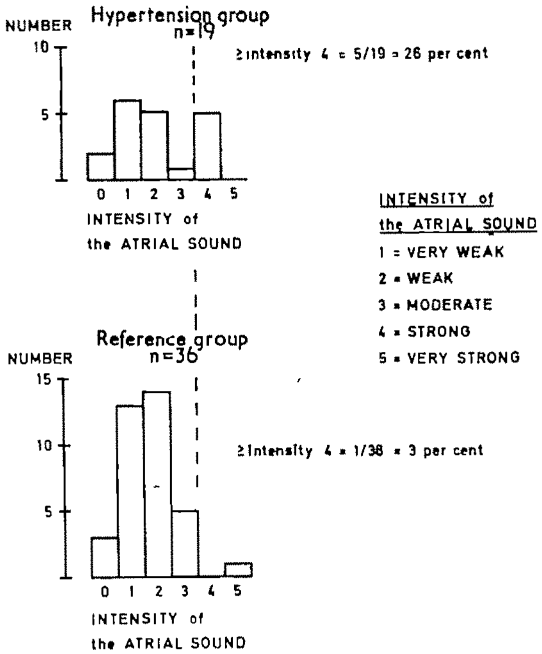

FIG. 4 *Distribution of atrial sounds of intensity 1 to 5 and the proportion of subjects with atrial sounds of intensity 4 and 5 in the hypertension and reference groups.*

## Signs of left ventricular hypertrophy and *a*/H ratio

The mean a/H ratio in the group of hypertensives with signs of left ventricular hypertrophy on orthogonal electrocardiogram ($\bar{x}=9{\cdot}0\%$, $s_{\bar{x}}=1{\cdot}0$, range 6 to 12, n=5) was significantly *lower* ($P<0{\cdot}01$) than in the group of hypertensives without signs of left ventricular hypertrophy ($\bar{x}=16{\cdot}1\%$, $s_{\bar{x}}=1{\cdot}8$, range 7 to 28, n=11). In this analysis two subjects with ventricular conduction defects were excluded.

## Blood pressure and type of heart involvement

There was no hypertensive showing both signs of left ventricular hypertrophy on orthogonal electrocardiogram and an abnormal *a* wave on the apex cardiogram or an abnormal atrial sound, i.e. signs of decreased distensibility of the left ventricle. Table 3 shows that hypertensives with signs of left ventricular hypertrophy on orthogonal electrocardiography had significantly higher ($P\leqslant0{\cdot}02$) casual diastolic blood pressure and significantly higher systolic ($P<0{\cdot}05$) as well as diastolic ($P\leqslant0{\cdot}01$) resting blood pressures than the group of hypertensives with signs of decreased left ventricular distensibility. There was no significant difference in heart rate between the two groups. If the two hypertensives with only abnormal atrial sound are removed from the group with *a*/H ratio greater than 15 per cent, there still was a significant difference ($P\leqslant0{\cdot}02$) in resting diastolic blood pressure between the two groups.

## Findings in three hypertensives with extremely high blood pressure

The casual blood pressures for these three subjects were 240, 268, and 250 mmHg (31·9, 35·6, and 33·3 kPa) systolic and 172, 164, and 160 mmHg (22·9, 21·8, and 21·3 kPa) diastolic, and the casual heart rates were 99, 72, and 89 beats/min. The third subject was treated immediately; the resting blood pressures for the other two were 196/130 mmHg (26·1/17·3 kPa) and 198/107 mmHg (26·3/14·2 kPa), respectively. All three had signs of left ventricular hypertrophy on orthogonal electrocardiogram ($R_x=2{\cdot}3$, $R_x+S_y=1{\cdot}9$, and $R_z=2{\cdot}5$ mV, respectively) and showed abnormal *a*/H ratios (50, 32, and 27%).

TABLE 3 *Blood pressure and heart rate in two groups of hypertensives with signs of left ventricular hypertrophy ($R_x>1{\cdot}8$ or $R_z>1{\cdot}3$ or $R_x+S_y>1{\cdot}9$ mV) and signs of lowered left ventricular distensibility (a/H ratio >15% or atrial sound of intensity 4 or 5)*

| | | | *Type of left ventricular involvement* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Hypertrophy No.=5/19* | | | *Lowered distensibility* No.=8/19* | | |
| | | | $\bar{x}$ | *Range* | $s_{\bar{x}}$ | $\bar{x}$ | *Range* | $s_{\bar{x}}$ |
| Casual | Systolic | | 206 | (216–198) | 3 | 193 | (220–164) | 7 |
| | Diastolic | (mmHg) | 125 | (132–118) | 2 | 116 | (122–104) | 2 |
| | Heart rate | (beats/min) | 79 | (114–61) | 9 | 87 | (108–61) | 6 |
| Resting | Systolic | | 171 | (192–146) | 7 | 137 | (172–111) | 8 |
| | Diastolic | mmHg | 107 | (120–98) | 4 | 86 | (107–64) | 5 |
| | Heart rate | (beats/min) | 59 | (74–50) | 4 | 60 | (73–43) | 3 |

*One subject with left bundle-branch block was excluded since left ventricular hypertrophy on orthogonal electrocardiography could not be analysed.

*Conversion from Traditional to SI Units:* 1 mmHg≈0·133 kPa.

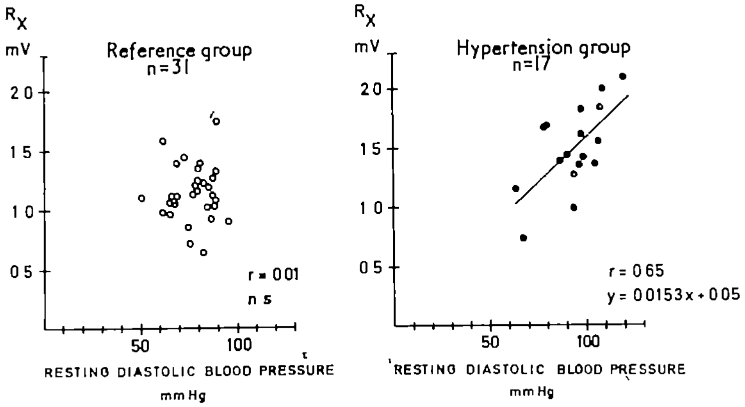

FIG. 5 *Relation between resting diastolic blood pressure and the amplitude of the R wave in lead X on orthogonal electrocardiogram. (Conversion from Traditional to SI Units: 1mmHg ≈ 0·133 kPa.)*

Two had abnormal atrial sounds as well. These three hypertensives with extremely high blood pressures thus showed signs of both left ventricular hypertrophy and decreased left ventricular distensibility.

### Relations between signs of left ventricular hypertrophy on orthogonal electrocardiogram, *a*/H ratio, and blood pressure

Linear correlation analysis for the relation between $R_x$ on orthogonal electrocardiogram and resting diastolic blood pressure in the hypertension group (see Fig. 5) gave $r=0{\cdot}65$ ($n=17$, $P<0{\cdot}01$). When the subjects with extremely high blood pressure were included in the linear regression analysis, the r value rose to 0·74. A significant positive correlation was also found in the hypertension group for the relation between $R_x$ and resting systolic blood pressure ($r=0{\cdot}50$, $n=17$, $P<0{\cdot}05$), as well as casual diastolic blood pressure ($r=0{\cdot}40$, $n=33$, $P<0{\cdot}05$). There was also a significant positive correlation in the hypertension group between resting diastolic blood pressure and $R_x+S_y$ ($r=0{\cdot}67$, $n=17$, $P<0{\cdot}01$) and spatial maximal amplitude ($r=0{\cdot}55$, $P<0{\cdot}05$). There was no significant linear correlation in the hypertension group either for the relation between casual systolic blood pressure and $R_x$ ($r=0{\cdot}03$, $n=33$), $R_x+S_y$ ($r=0{\cdot}01$), $R_z$ ($r=0{\cdot}33$), or spatial maximal amplitude ($r=0{\cdot}05$). In the hypertension group $R_x$ above 1·8 mV was only seen when the casual diastolic pressure exceeded 110 mmHg (14·6kPa) or resting diastolic pressure exceeded 95 mmHg (12·6 kPa). In the reference group there was no significant correlation of $R_x$ either with casual or with resting blood pressure. No significant linear correlations of a/H ratio to blood pressure were found either in the hypertension, or in the reference group.

## Discussion

The subjects of the study were selected at random from a total male population. As most of the variables studied are age and sex dependent, we chose to study normotensive and hypertensive men of the same age. To our knowledge, no previous study of cardiac function in relation to blood pressure has used these quantitative, non-invasive methods in subjects derived from a screening examination for blood pressure in a total population.

In the hypertension group, orthogonal electrocardiography showed a higher prevalence of signs of left ventricular hypertrophy than conventional electrocardiography. Since the prevalence of signs of left ventricular hypertrophy in the reference group was the same with both methods, orthogonal electrocardiography seems to be a better method for discrimination of left ventricular hypertrophy in hypertension. Furthermore, orthogonal electrocardiography is more practical, since simple QRS amplitude measurements are sufficient, while on conventional electrocardiography, QRS amplitude measurements have to be combined with other criteria, such as ventricular activation time or ST or T changes for the diagnosis of left ventricular hypertrophy (Sokolow and Lyon, 1949). Measurement of the spatial maximal amplitude was found redundant, as had also been found in a previous study (McCaughan *et al.*, 1973).

Atrial sounds can be recorded in the majority of normal individuals aged 50 (Rectra *et al.*, 1972) and this is also evident from the present study. This means that the atrial sound as well as the *a* wave in the apex cardiogram has to be in some way quantified to be of use in differentiating normal from abnormal. The judgement had to depend on the empirical judgement of one of the authors. Even if the hypertensives with only abnormal atrial sound are removed from the hypertensives with *a*/H ratio greater than 15 per cent the figures still allow the separation of two types of heart involvement in hypertension. Apex cardiogram and recording of atrial sounds complement each other, since the overlapping between the two methods was less than often claimed (Tavel *et al.*, 1965; Epstein *et al.*, 1968; Tavel, 1974). Different filter properties of the thoracic wall for sound and volume displacement as well as the difference in origin mechanisms for the *a* wave and the atrial sound may explain the finding that there was no total overlapping.

The morphological evidence of left ventricular hypertrophy is increased left ventricular mass (Romhilt and Estes, 1968). Mass itself has been shown to be a poor predictor of distensibility, while wall thickness was an excellent predictor (Grossman *et al.*, 1974). The mean *a*/H ratio in patients with signs of left ventricular hypertrophy on conventional electrocardiography has been shown to be significantly higher than in patients without left ventricular hypertrophy (Gibson *et al.*, 1974). In the present study mean *a*/H ratio was significantly lower in hypertensives with signs of left ventricular hypertrophy on orthogonal electrocardiography than in hypertensives without these signs, which is in contrast to the above-mentioned studies. Hypertensives in the present study with signs of left ventricular hypertrophy had no signs of decreased left ventricular distensibility. One reason for this might be that the hypertrophy was not of the degree that gives a sufficient increase in wall thickness to give distensibility changes. The degree of hypertrophy in our hypertensives was probably mild compared with the hypertrophy in the above-mentioned studies. Another explanation could be that a relative strengthening of the systolic wave in relation to the *a* wave resulting from the hypertrophy could have led to a decrease in the *a*/H ratio. In two of the three subjects with extreme levels of casual blood pressure the decreased left ventricular distensibility might have been caused by left ventricular hypertrophy, namely in Cases 1 and 3 where the QRS amplitudes on orthogonal electrocardiography were very large.

The signs of decreased left ventricular distensibility in the hypertension group could not be related to hypertrophy, at least not electrocardiographically proven. Decreased distensibility of the left ventricle is not a specific finding of left ventricular hypertrophy but is also found in ischaemic heart disease (Voigt and Friesinger, 1970; Martin, Shaver, and Leonard, 1972). There was, however, no subject in the hypertension group with symptoms of angina pectoris as judged by one of the authors (G.B.). In any consideration of ventricular distensibility, it must be borne in mind that the diastolic pressure-volume curve is not linear. Thus, a structurally normal ventricle may exhibit the same low distensibility as a scarred or hypertrophied ventricle if its filling pressure is raised sufficiently (Levine, 1972). Another explanation for the signs of decreased left ventricular distensibility could thus be abnormal distension of the left ventricle during the atrial contraction partly caused by increased central blood volume. Increased central blood volume has been described in essential hypertension (Ulrych *et al.*, 1969; Ellis and Julius, 1973).

A model of the circulation has been described in which hypertension initially resulting from increased blood volume and/or cardiac output can subsequently become converted to a hypertension with high peripheral resistance and normal or lowered cardiac output (Guyton and Coleman, 1969). In the present study the resting blood pressure was returned to normal in the hypertensives with signs of decreased left ventricular distensibility, but not in the hypertensives with signs of left ventricular hypertrophy. This might suggest that the former group is in an earlier state of hypertensive disease while the other is in a later state with raised peripheral resistance. Whether the former group will pass over into a hypertension of the latter type or not must be studied prospectively. In advanced left ventricular hypertrophy an abnormal *a* wave in the apex cardiogram is a very common finding (Tavel *et al.*, 1965; Epstein *et al.*, 1968). It might be that an initial abnormal *a* wave caused by volume stiffness of the left ventricle can return to normal, and then when the left ventricular hypertrophy becomes pronounced or fibrosis is added, structural changes in the left ventricular wall can again give rise to an abnormal *a* wave.

The correlation coefficient between blood pressure and amplitude measurements on orthogonal electrocardiography were higher in the present study than in a previous one (McCaughan *et al.*, 1973) ($r=0{\cdot}65$ for $R_x$ in the present study, compared with $r=0{\cdot}23$ for $R_z$ in the previous investigation). In the latter investigation, however, a group of patients with severe hypertensive heart disease had large $R_z$ amplitudes and a concomitant decrease in $R_x$. The homogeneity of our hypertension group of subjects with early hypertension probably implies that the amplitude of the $R_x$ will reflect the degree of left ventricular hypertrophy better than will $R_x$ in the latter investigation.

In the present investigation there was better correlation between QRS amplitude measurements and resting blood pressure than to casual blood pressure, indicating that resting blood pressure better reflects the degree of pressure load leading to left ventricular hypertrophy. The fact that these hypertensives were untreated and never had been treated probably also implies that the blood pressures were more representative of the pressure load on the left ventricle than blood pressure in treated patients can be.

It is evident from the present study that the orthogonal electrocardiogram, the apex cardiogram, and the recording of atrial sounds complement each other in the investigation of hypertensive heart disease. The combination of the three methods made it possible to detect heart involvement in the majority of hypertensive subjects. The numbers with full studies are, however, small. Prospective follow-up must be undertaken in larger groups to study the haemodynamic pattern and prognosis in hypertensives with the different abnormal findings. These studies are now proceeding.

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# Linear densities in mitochondria of human myocardial cells[1]

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*Ultrastructural study of myocardial biopsies from 5 patients who underwent myocardial revascularization procedures because of impending infarction showed mitochondria with linear densities. These densities, which occupied the intracristal space, appeared to have a high protein but low mineral content. It is suggested that linear densities may be an expression of severe, acute myocardial cell injury.*

Linear densities in mitochondria have been described by Denker, Bergman, and Nachlas (1969) and Dusek, Rona, and Kahn (1971) in association with ischaemic injury to the heart of experimental animals. In addition, a number of other pathological conditions of muscle cells in man have been shown to be associated with such densities (Fisher and Danowski, 1969; Sluga and Monneron, 1970; Tandler *et al.*, 1970; Woodhouse and Burston, 1969).

This paper deals with observations in five patients who were found to have linear densities in mitochondria of cardiac muscle cells obtained from the left ventricle at the time of cardiac surgery. The conclusion is drawn that these findings are likely to represent a cumulative effect of repetitive periods of ischaemic injury to the myocardium.

## Patients and methods

The five patients reported in this paper were admitted to the Cardiovascular Surgery Service at the University of Wisconsin Hospitals for coronary revascularization procedures. The relevant clinical data of these patients are summarized in Table 1.

Full thickness biopsies were taken in all patients from the anterior free wall of the left ventricle, near the apex using a nitrogen gas driven drill (Braimbridge and Niles, 1964). In this group of patients, no attempt was made to remove material from the ischaemic zone of the left ventricle for biopsy but it is likely that in Case 2 the control biopsy was taken from an injured zone as judged by the standard 12 lead scalar electrocardiogram, arteriogram, and operative findings. In 3 of the patients, biopsies were obtained at the beginning (control) and at the end (experimental) of cardiopulmonary bypass. In Case 2 only a pre-bypass specimen was obtained, while in another (Case 4) a single post-bypass biopsy was obtained. Care was exercised to assure that both biopsies were taken from adjoining areas of the left ventricular free wall near the apex, whose blood supply was the left anterior descending artery.

The biopsies were fixed within 30 seconds of removal from the heart by immersion into cold 4 per cent formaldehyde, 2 per cent glutaraldehyde, 0·5 mmol CaCl, in 0·1 mol Na cacodylate at *p*H 7·2. The formaldehyde was diluted from 10 per cent formaldehyde prepared by alkaline depolymerization of paraformaldehyde. After primary fixation, the tissue was diced and washed overnight at 4°C in three changes of 0·1 mol Na cacodylate buffer at *p*H 7·2. The tissue was then post-fixed in 2 per cent osmium tetroxide for two hours at room temperature, dehydrated in ethanol, contrasted in block with ethanolic uranyl acetate, and embedded in an Epon-Araldite mixture. Two to five blocks were obtained from each biopsy, and all were examined. Only central portions of the biopsy material were studied in order to avoid the possibility of examining tissue that was damaged as a result of the biopsy procedure. One hundred to three hundred sections were studied from each block obtained at two different levels within the

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TABLE 1 *Summary of clinical data*

| *Case no.* | *Age (y)* | *Sex* | *Pre-infarction angina* | *Preop ECG* | *Coronary arteriographic findings* | *Surgical procedure and findings* | *Total pump time (min)* | *Aortic cross-clamp time* | *Post-operative course* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 51 | M | Yes | Inferoseptal infarction | 99% stenosis RCA<br>90% stenosis LAD<br>50% stenosis circ | 3 vessels bypassed | 171 | 4 times, 33 min total | Uneventful |
| 2 | 57 | M | Yes | T waves negative in I, aVL, V2–V5 | 95% stenosis LAD | LAD bypassed; anterior wall motion poor with dusky appearance | 127 | 5 times, 42 min total | Uneventful |
| 3 | 42 | M | Yes | Normal | 95% stenosis LAD | LAD bypassed; good left ventricular motion | 104 | 3 times, 28 min total | Developed anteroseptal wall infarction, with Q waves in V1–V3 and negative T waves in I, aVL, V2–V5 |
| 4 | 53 | M | Yes | ST depressed 0·5 mm in V3–V5, T inversion in I and aVL | 95% stenosis LAD<br>75% stenosis RCA<br>100% stenosis circ | 3 vessels bypassed; cardiac action poor, patient expired in OR | 533 | 8 times, 64 min total | — |
| 5 | 47 | M | Yes | Normal | 99% stenosis RCA<br>95% stenosis LAD<br>75% stenosis circ | 3 vessels bypassed | 331 | 11 times, 93 min total | Uneventful |

RCA=right coronary artery; LAD=left anterior descending coronary artery; circ=circumflex coronary artery; OR=operating room.

TABLE 2 *Summary of ultrastructural findings*

| *Case no.* | *Pre-bypass biopsy* | *Post-bypass biopsy* |
|---|---|---|
| 1 | Normal structure | Showed considerable intracellular swelling, loss of glycogen particles, and moderate mitochondrial swelling; linear densities were present in about 20% of mitochondrial profiles |
| 2 | Abnormal myocardial cell morphology, including some intracellular swelling, some loss of glycogen particles, and moderate mitochondrial swelling; linear densities were present in about 10% of mitochondrial profiles | None obtained |
| 3 | Normal structure | Moderate intracellular swelling, considerable loss of glycogen particles, severe mitochondrial swelling with clearing of matrix and loss of cristae; linear densities were present in about 50% of mitochondrial profiles |
| 4 | None obtained | Severe intracellular swelling, total loss of glycogen particles, badly swollen and disrupted mitochondria, with clearing of matrix and loss of cristae; linear densities were present in about 60% of mitochondrial profiles |
| 5 | Normal structure | Intracellular swelling, almost total loss of glycogen particles, and severe mitochondrial swelling with loss of cristae and matrix density; linear densities were present in nearly 80% of mitochondrial profiles |

same block. The frequency of the appearance of linear densities within mitochondrial profiles was estimated from 18 micrographs taken at random from these sections (Table 2) which were cut on a Porter-Blum MT-2 ultramicrotome, further contrasted with lead citrate, and studied in a Hitachi HU-11B electron microscope.

Micro-incineration, similar to that described by Shen and Jennings (1972), was employed in an attempt to gain information on the mineral composition of the linear densities and amorphous granules observed. Sections of tissue were mounted on grids coated with silicon monoxide, routinely stained, and examined and photographed in the electron microscope. Diagrams were made of the grids to permit location of the area photographed after

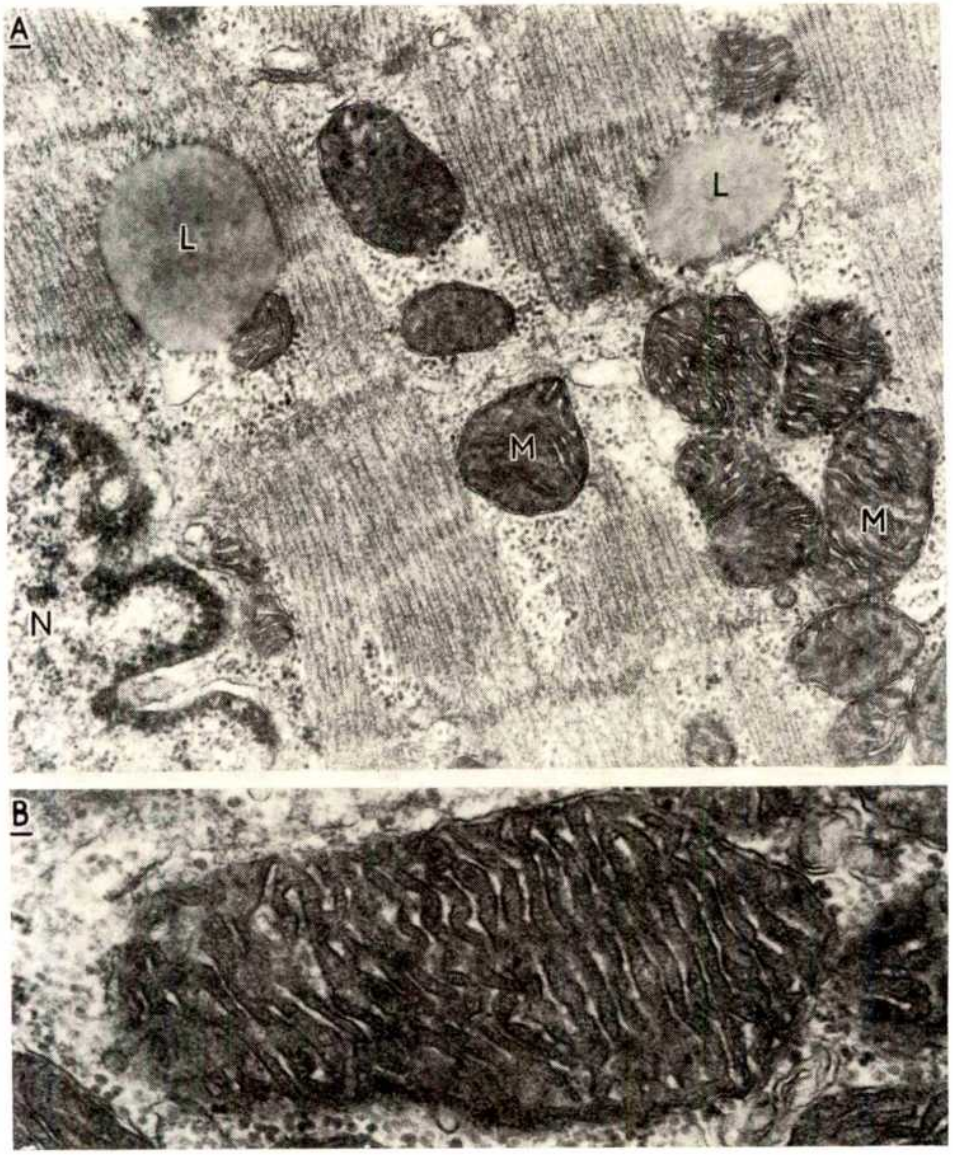

FIG. 1 (A) *An electron micrograph of left ventricular muscle obtained from Case 5 before initiation of cardiopulmonary bypass, showing abundant glycogen particles and lack of intracellular swelling. A portion of a nucleus is visible (N), and lipid droplets, seen frequently in human myocardial cells, are apparent (L). The mitochondria (M) appear dense and well organized. (×31 900.) (B) A high magnification view of a mitochondrion from cardiac muscle obtained from Case 5 before initiation of cardiopulmonary bypass. Numerous, well-organized cristae are apparent, demarcating a dense appearing matrix. The area of the mitochondrial profile occupied by the transparent intracristal space appears to be approximately equal to area occupied by the dense matrix. (×60 000.)*

incineration. After photography, the grids were subjected to periods of heat in air sufficient to bring the grids to a dull red glow. The grids were re-examined at three-minute intervals, and the degree of destruction observed. This procedure was continued until complete destruction of the sections occurred, and tissue detail was totally lost.

## Results

Examination of myocardial cells obtained from the pre-bypass biopsy material showed normal human myocardial ultrastructure (except from Case 2), with abundant glycogen particles, little or no intracellular swelling, and dense, well-organized mitochondria (Fig. 1A). The mitochondrial matrix

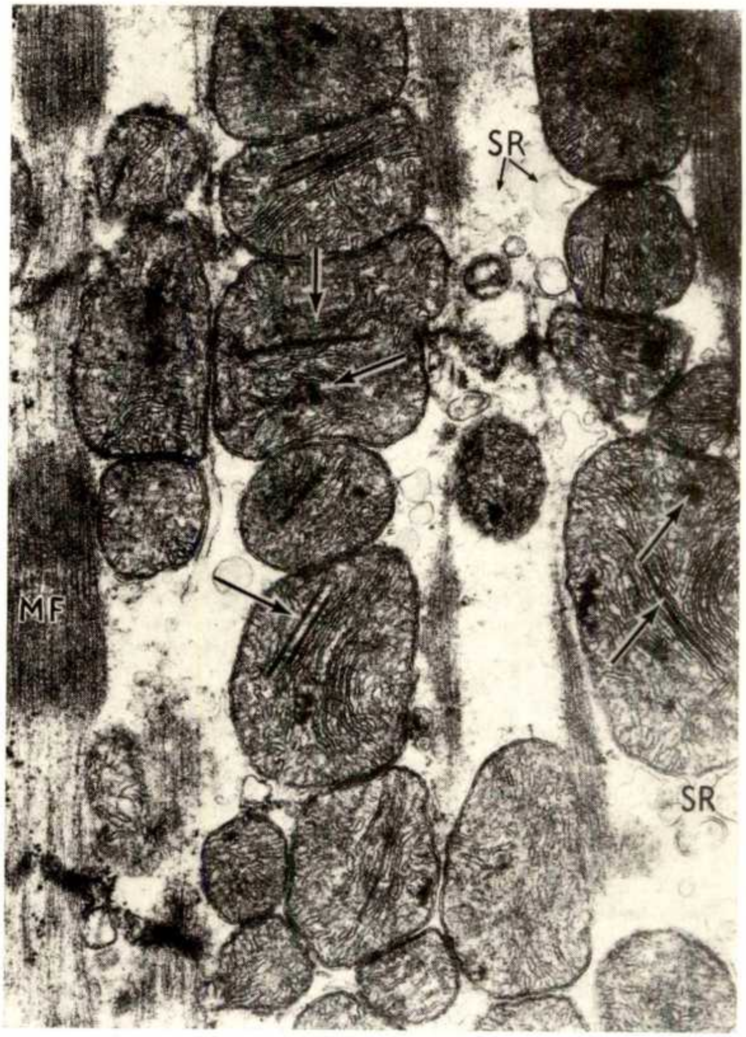

FIG. 2 *An electron micrograph of left ventricular muscle obtained after cardiopulmonary bypass in Case 1, showing the morphological changes associated with ischaemic injury, and, in addition, linear densities in mitochondria. Considerable intracellular swelling is obvious, along with vesiculation of the sarcoplasmic reticulum (SR) and extreme elongation of the sarcomeres (MF). Glycogen particles are scarce. The mitochondria appear swollen, with reduction of matrix density. Linear densities and amorphous dense granules can be seen in several of the mitochondria (arrows). (×26 600.)*

material appeared dense and the intracristal space transparent, with the two compartments occupying approximately equal volumes (Fig. 1B). Varying degrees of cellular change were seen in the biopsy specimens obtained after bypass. These are summarized in Table 2. Intracellular swelling, loss of glycogen particles, and mitochondrial swelling were commonly noted in the post-bypass samples, though in case 2 considerable cellular swelling and linear densities were present in the pre-bypass sample of myocardium. In three cases (Cases 1, 4, and 5), more severe damage was apparent, with appearance of vesiculation of the sarcoplasmic reticulum, extreme cellular swelling, and margination of nuclear chromatin.

In all instances, linear densities and amorphous granules were noted in mitochondria of myocardial cells from post-bypass biopsies. The frequency of this finding varied from patient to patient (Table 2) and appeared to correlate best with the degree of overall cellular damage. Thus, in the more severely damaged myocardial cells, a larger number of mitochondria were found to contain linear densities. However, this was not true of the number of linear densities in each mitochondrial profile. In general, one or two linear densities were found in any particular mitochondrial profile, regardless of the degree of cellular damage. Frequently, amorphous granules were also observed, often in the same mitochondria containing linear densities. They were more common in severely damaged tissue (Fig. 2). The distribution and frequency of these alterations were uniform throughout the samples studied.

When studied at higher magnification, the linear densities appeared to consist of electron opaque material deposited between a pair of cristal membranes, in the intracristal spaces (Fig. 3A, B, C). The contrast of this material was enhanced by staining with lead citrate (Fig. 3B, and C). In favourable sections, an apparent core was observed, appearing as a fifth electron dense line midway between the four electron dense lines representing the cristal membranes (Fig. 3B). Resolution of this core into individual subunits, such as the intracristal rods reported by Hall and Crane (1971), was suggested in some instances (Fig. 3C), but could not be consistently obtained. Measurements of the intracristal space indicated that the spaces occupied by linear densities were slightly narrower (approximately 140Å) than those without such densities (about 200 to 400Å). The linear nature of these structures suggests that the dense material imparts a rigidity to the occupied cristae.

Microincineration studies of sections showed an even loss of structure, with increasing duration of incineration. Membranes disappeared rapidly, leaving rows of electron dense dots which delineated the former location of these structures. Amorphous granules and mitochondrial cristae could not be recognized after 6 minutes of incineration while outer mitochondrial membranes and linear densities required 9 minutes of incineration before they too disappeared. Once all recognizable morphology was destroyed, no deposits that corresponded to the location of the linear densities or amorphous granules could be seen.

## Discussion

The ultrastructural findings reported in this paper indicate that human myocardial cells are altered to varying degrees when subjected to ischaemia. In the post-bypass sample of heart muscle, structural damage was severe, suggesting that the added periods of ischaemia and reperfusion, a necessary part of the surgical procedure, contributed significantly to the production of these abnormalities. That cardiopulmonary bypass with aortic cross-clamping results in intracellular swelling, loss of

FIG. 3 (A) *An electron micrograph of left ventricular muscle obtained after cardiopulmonary bypass in Case 5, showing two typical mitochondria that are swollen with loss of matrix density and cristae. Several linear densities are apparent, and a core or central filament can be observed (arrows) in favourable orientations of the densities. (×175 000.) (B) Linear densities in mitochondria from post-cardiopulmonary bypass muscle samples of Case 3 are shown at high magnification. The dense material appears to be deposited in the intracristal space, and to have a core or central filament (single arrows). The upper density appears to be interrupted at one point, and then to continue without the core or dense material (double arrow). This section did not receive additional contrasting with lead citrate. (×243 000.) (C) Further examination at high magnification (Case 5) shows, in this instance, the core of the density to be resolvable into dense dots or rods (arrows) similar in appearance to the structures reported by Hall and Crane (1971) in isolated beef heart mitochondria. This section did receive additional contrasting with lead citrate. (×180 000.)*

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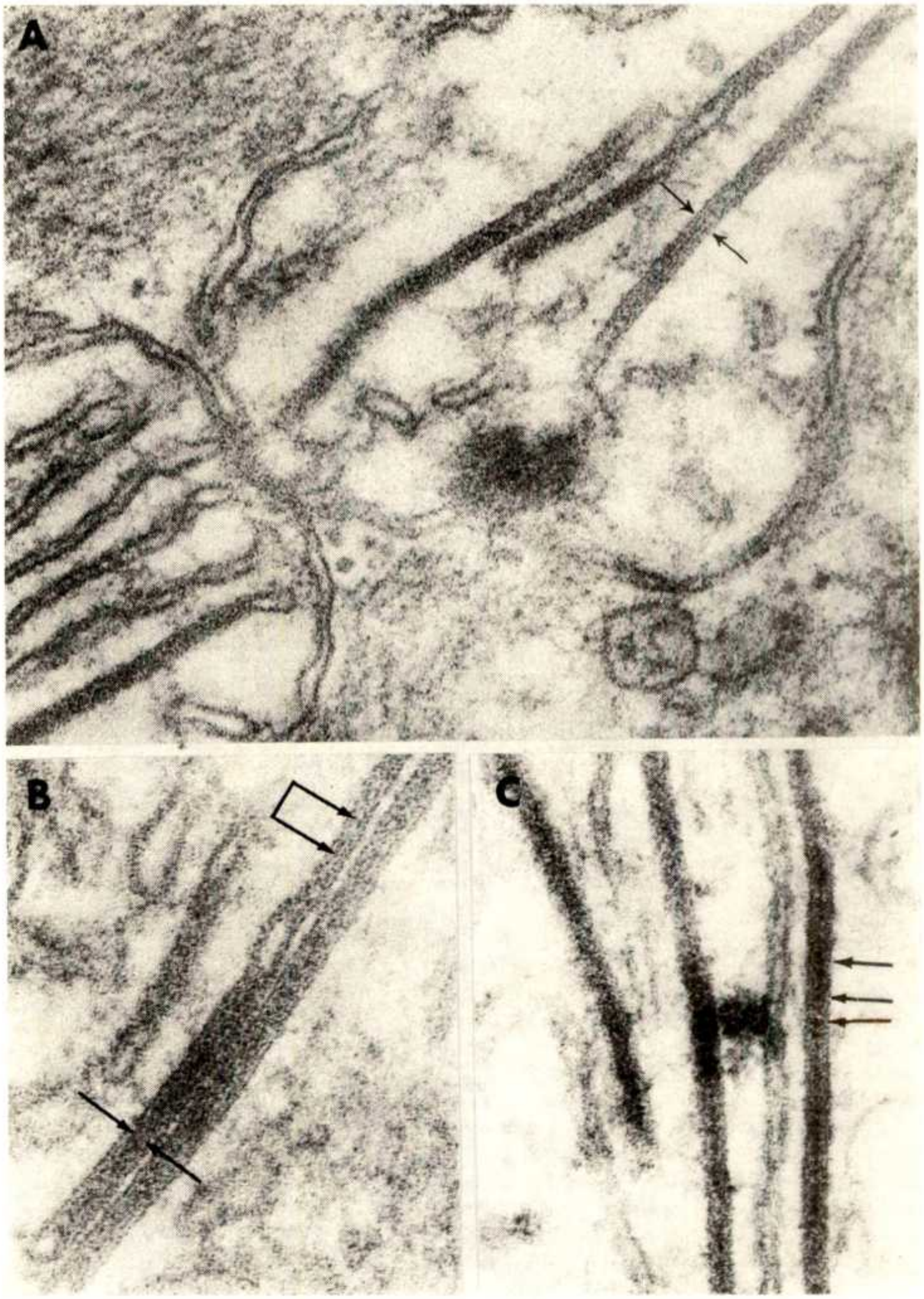
glycogen particles, and mitochondrial alteration is well documented (Bellotti *et al.*, 1974; Bittar *et al.*, 1974; De Gasperis, Miani, and Donatelli, 1970). However, linear densities within myocardial mitochondria after cardiopulmonary bypass have not been previously described.

In Case 2 these changes were observed in the pre-bypass biopsy. In this case, the preoperative electrocardiogram, and observation of the anterior wall of the left ventricle at operation, suggested that this portion of the left ventricle was indeed ischaemic. This finding indicates that myocardial



ischaemia in man results in similar cellular alterations as seen in experimental animals. In three other cases where pre-bypass biopsies were obtained, these were not taken from ischaemic muscle. Ultrastructural examination confirmed that they were essentially normal. Since the post-bypass biopsies of all patients showed significant morphological alterations, which included linear densities in mitochondria, it appears that the bulk of cellular damage seen was induced by the cardiopulmonary bypass procedure. This is not surprising since the heart was subjected to periods of ischaemia and reperfusion, conditions known to result in pronounced cellular damage (Herdson, Sommers, and Jennings, 1965; Kloner *et al.,* 1974; Whalen *et al.,* 1974). These findings appeared identical to those induced by myocardial ischaemia (Case 2) alone. Though linear densities in mitochondria have not been described as a feature of the morphological alterations induced by either cardiopulmonary bypass (Bellotti *et al.,* 1974; Bittar *et al.,* 1974; De Gasperis *et al.,* 1970) in man, or by ischaemia followed by reperfusion in animals (Herdson *et al.,* 1965; Kloner *et al.,* 1974; De la Iglesia and Lumb, 1972), they have been associated with acute infarction in experimental animals (Denker *et al.,* 1969; Dusek *et al.,* 1971). It is thus possible that linear densities in human mitochondria may be a feature of acutely ischaemic myocardial cells, whether induced by chronic degenerative processes or surgical interventions, or a combination of both.

Since linear densities have been shown to occur under conditions other than ischaemia, such as malignant hypertension (Huttner, Rona, and More, 1971), metastatic calcification in a patient with renal failure (Woodhouse and Burston, 1969) and in several myopathies (Fisher and Danowski, 1969; Sluga and Monneron, 1970), it appears that other causes of cell injury can result in similar mitochondrial alterations. However, it is interesting to note that these findings have all arisen from pathological conditions of muscle cells, whether cardiac or skeletal. Structures of similar appearance have also been found in apparently normal mitochondria obtained from several non-mammalian sources (Munn, 1974).

It is possible that linear densities result from calcium deposition as suggested by Woodhouse and Burston (1969). However, the microincineration of grids with sections containing linear densities did not support this idea. It may be that the amount of calcium deposited was insufficient to leave detectable ash. Another explanation is that these densities may represent protein deposition or accumulation in the intracristal space (Dusek *et al.,* 1971; Fisher and Danowski, 1969; Sluga and Monneron, 1970). The observation that exposure to lead citrate results in increasing electron opacity supports this idea. Whether or not the 'intracristal rods' reported by Hall and Crane (1971) in isolated beef heart mitochondria are structures similar to or identical to the linear densities reported here is uncertain. Hall and Crane (1971) showed that aldehyde fixation was necessary to visualize 'intracristal rods' and, therefore, concluded that they were protein in nature.

Regardless of the nature of these densities, their appearance in mitochondria in a variety of pathological conditions suggests that they may reflect a common mitochondrial lesion induced by various conditions. Insight into the nature of linear densities may contribute to a better understanding of the pathogenesis of cell injury.

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# Effect of acute administration of propranolol on ventricular function in hypertrophic obstructive cardiomyopathy measured by non-invasive techniques[1]

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*Seventeen patients with hypertrophic obstructive cardiomyopathy, were studied using non-invasive techniques before and after the intravenous injection of 5 mg propranolol. The following were analysed: left ventricular ejection time index, derived from the carotid pulse and heart rate; the isovolumic relaxation time, derived from the apex cardiogram and phonocardiogram; the diastolic closure rate of the mitral valve; and left ventricular diameters, systolic and diastolic, both measured by echocardiography.*

*Propranolol produced shortening of the isovolumic relaxation time, increase in both the diastolic closure rate of the mitral valve and left ventricular systolic and left ventricular diastolic diameters. These results show that propranolol increases the rate of filling and the volume of the left ventricle, indicating that an improvement in distensibility is produced by beta-adrenergic blockade.*

Since the first description of hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subaortic stenosis (Brock, 1957; Braunwald *et al.*, 1960; Goodwin *et al*, 1960), advances have been made in the treatment of this disease, both medically and surgically (Flamm, Harrison, and Harcock, 1968; Bentall *et al.*, 1965; Cooley *et al.*, 1967).

The acute effects of beta-adrenergic blockade with propranolol in HOCM suggest that it produces an improvement in distensibility and filling of the left ventricle (Webb-Peploe *et al.*, 1971). Propranolol has been thought to be the treatment of choice (Hubner *et al.*, 1973).

Because most drug studies involve using invasive techniques, they are not applicable for the repeated assessment of patients, and therefore the beneficial effects of propranolol in HOCM must be judged mainly by symptomatic assessment of the patient (Cohen and Braunwald, 1967; Hubner *et al.*, 1973).

The purpose of the present paper is to study the acute effect of propranolol (5 mg intravenously) in HOCM, using simple bedside non-invasive techniques, and see if these methods are sensitive enough to detect the haemodynamic benefit of beta-blockade.

## Subjects and methods

The present series consists of 17 adult patients with HOCM. Eleven were women and six men. The diagnosis was proven by previous catheterization and angiocardiography.

All patients stopped propranolol therapy 4 to 7 days before the investigation, which was carried out in the early afternoon with the patient lying supine.

### Non-invasive studies

These were recorded using a 6-channel Cambridge Machine (model 72112, Cambridge Scientific Instruments, England), at a paper speed of 100 mm per second. The sensitivity settings of the control study were used in the post-propranolol state. The following studies were made.

(1) **Electrocardiogram** A bipolar lead showing clearly the beginning of the QRS complex was recorded simultaneously with the rest of the tracing.

(2) **Phonocardiogram** A clear aortic component

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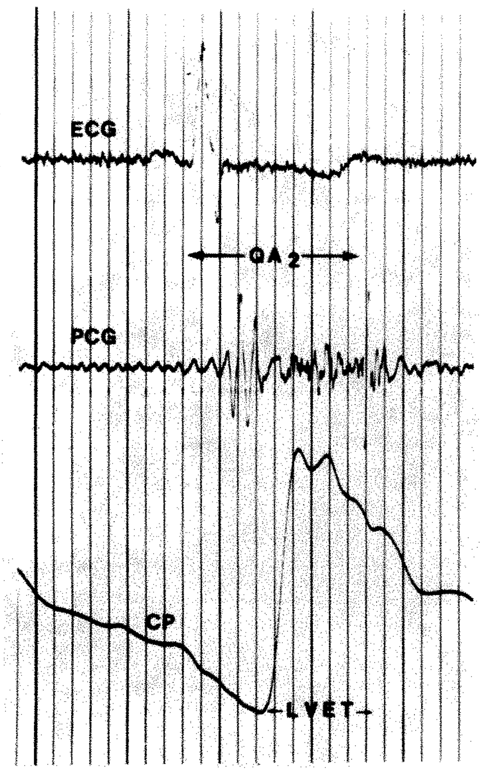

of the second heart sound was obtained. Phonocardiograms were recorded at the third and fourth intercostal spaces along the left sternal border using suction microphones with high (band with 450 and 1·000 Hz) frequency filters.

**(3) Carotid pulse** A clear upstroke and dicrotic notch was obtained.

**(4) Apex cardiogram** A well-inscribed 'O' point was obtained. Recordings were made with the patient in the left anterior oblique position.

Carotid and apex cardiogram tracings were obtained with a hand-held polythene funnel connected to a piezoelectric transducer with a pulse amplifier of time constant 1·6 s, band with 0·1 to 100 Hz.

**(5) Echocardiography** (12 patients only). Echocardiograms were made using an Ekolone 20 diagnostic ultrasound (frequency 2·25 MHz, repetition frequency 1000/s), with polaroid photography.

The following measurements were analysed:

*(A) Left ventricular ejection time index (LVETI)*, taken as the time (in ms), from the carotid upstroke to the dicrotic notch (LVET). The values were

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FIG. 1 *Simultaneous tracing of the electrocardiogram (ECG), phonocardiogram (PCG), and carotid pulse (CP), illustrating the measurement of left ventricular ejection time (LVET).*

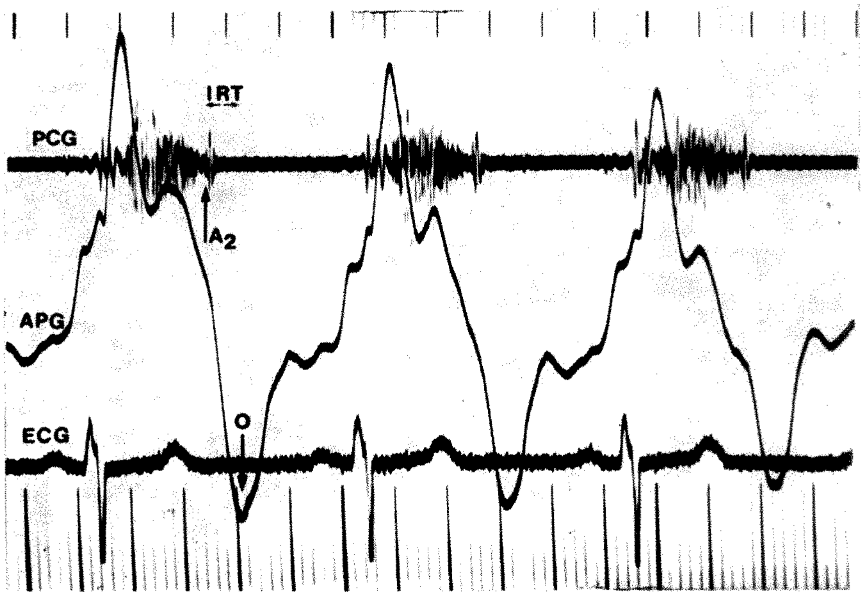

FIG. 2 *Simultaneous tracing of the electrocardiogram (ECG), phonocardiogram (PCG), and apex cardiogram (APG), illustrating the measurement of isometric relaxation time (IRT).*

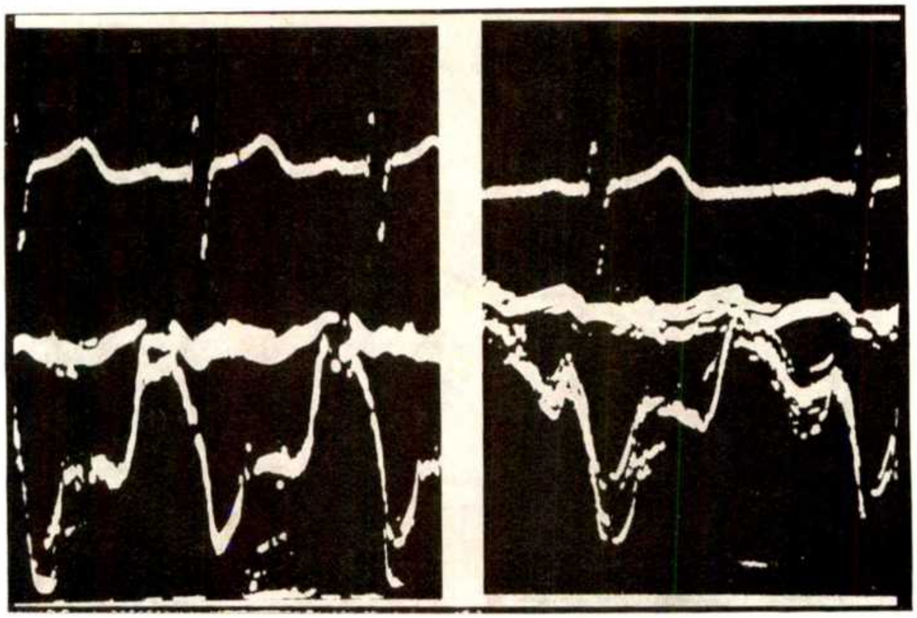

FIG. 3 *Mitral echogram before and after propranolol.*

corrected for heart rate (LVETI), using the regression equation of Weissler, Harris, and Schoenfeld (1968) (Fig. 1).

*(B) Isometric relaxation time (IRT)* was expressed in ms, and measured as the time from the aortic component of the second heart sound to the 'O' point of the apex cardiogram (Fig. 2).

*(C) Diastolic closure rate (DCR)* of the mitral echogram was expressed in mm/s and measured in the usual way, as described by Edler (1967) (Fig. 3).

*(D) Left ventricular diameters by echocardiography* Diastolic diameter was measured in cm as the distance between the septal and left ventricular echoes at the moment of the R wave inscription of the electrocardiogram. The systolic diameter was measured in the same way but when both echoes were closest to each other (Pombo, Troy, and Russell, 1971; Popp *et al.*, 1973) (Fig. 4).

*(E) Heart rate* This was measured in beats per minute.

## Results

The results of the present study are summarized in the Table. After propranolol, heart rate decreased from $79 \pm 18$ beats per minute in the control state to $67 \pm 9$. This change is statistically significant ($P < 0{\cdot}005$).

Left ventricular ejection time index (LVETI) became shorter after the drug administration (from $428 \pm 33$ to $419 \pm 37$ ms) ($P < 0{\cdot}05$).

Because all patients in the present study had left ventricular outflow obstruction as shown by previous catheter data not included in the paper, the reduction of LVETI after propranolol may be related to a decrease in left ventricular obstruction, a well-known effect of propranolol in this disease.

The acute administration of 5 mg propranolol did dilate the left ventricle as judged by the echocardiographic increase of left ventricular diameters, both in systole (from $3{\cdot}4 \pm 8$ cm to $3{\cdot}7 \pm 8$ cm; $P < 0{\cdot}05$) and diastole (from $4{\cdot}2 \pm 8$ cm to $4{\cdot}7 \pm 9$ cm; $P < 0{\cdot}05$).

Finally the two parameters that reflect, in the present study, the rate of ventricular filling did change, indicating an improvement in ventricular filling as reflected by a reduction of the isovolumic relaxation time from $145 \pm 9{\cdot}5$ ms to $122 \pm 10{\cdot}3$ ms; thus, the left ventricle needed less time to relax after propranolol. At the same time the diastolic closure rate of the mitral echogram was accelerated from $47 \pm 4$ mm/s to $76 \pm 8$ mm/s, this change being statistically significant ($P < 0{\cdot}001$).

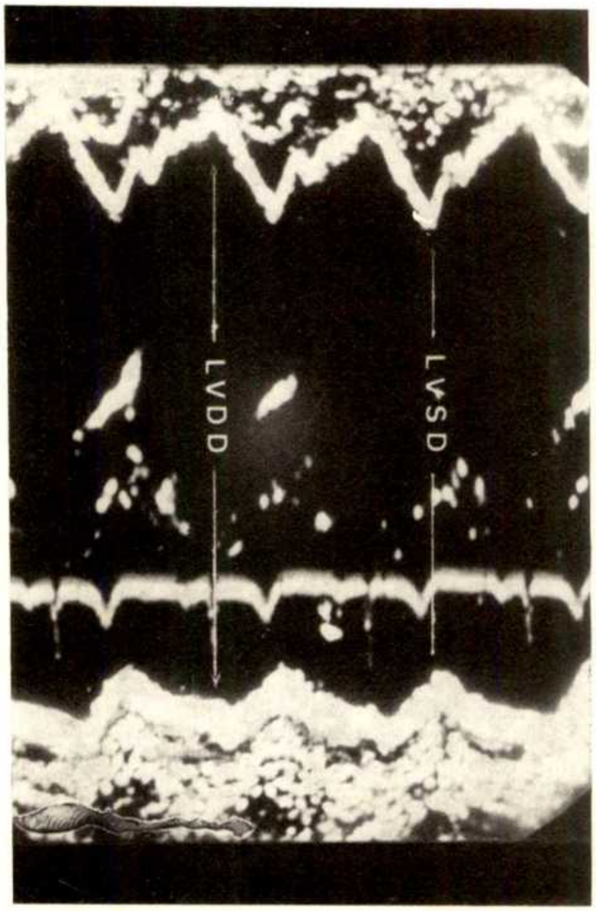

FIG. 4 *Left ventricular diameters by echocardiography. Left ventricular diastolic diameter (LVDD) and left ventricular systolic diameter (LVSD).*

No patient had any side effect caused by the administration of 5 mg propranolol during the study. The blood pressure did not change significantly from the control state.

## Discussion

Though propranolol has been the drug of choice in the medical treatment of HOCM for almost a decade (Flamm *et al.,* 1968; Harrison *et al.,* 1964), there is still some disagreement as to its place in the management. Some authors (Goodwin and Oakley, 1972) suggest that it should be given to all patients, seven those who are asymptomatic, while other suggest that it should be reserved only for those who have not responded to cardiac surgery (Rookmaker *et al.,* 1971).

This controversy may very well be because of the lack of objective data at the bedside on which to judge the haemodynamic effects of propranolol.

Of patients with HOCM 14 per cent are asymptomatic or have symptoms that are difficult to assess (Hardarson *et al.,* 1973). In this group of patients it is difficult or impossible to judge clinically the effects of propranolol. Such effects can be measured by haemodynamic studies (Kristinsson, 1971), but this method cannot be repeated serially. Therefore, non-invasive techniques, in the assessment of propranolol in HOCM, may have practical importance.

In a previous publication from this laboratory (Hubner *et al.,* 1973), it was shown that the haemodynamic effects of oral propranolol (320 mg daily) on a long-term basis could be assessed by non-invasive methods. In the present study a similar approach was taken to see if 5 mg propranolol given intravenously would produce effects which could be measured by non-invasive methods.

The results of the present study are summarized in the Table.

The bradycardic effects of propranolol are well known and need no further comment. The LVETI is abnormally prolonged in HOCM, and is related to the outflow tract obstruction (Hardarson, 1974); it became shorter after intravenous propranolol. (From 428 ±33 ms to 419 ±37 ms; P < 0·05.)

Two explanations can be given for this effect. Because propranolol reduces left ventricular outflow tract obstruction (Kristinsson, 1971) and LVETI is related to it (Hardarson, 1974), it is possible that the shortening of LVETI encountered in the present study may reflect the amelioration of the outflow obstruction produced by propranolol. An alternative explanation is that the shortening of LVETI reflects the reduction of contractility produced by propranolol (Epstein and Braunwald, 1966), despite an improvement in ventricular filling.

The shortening of LVETI observed in the present study is in contrast to the prolongation of left ventricular ejection time reported by Hubner *et al.* (1973) in HOCM treated with daily doses of 320 mg propranolol. In the latter situation the further prolongation of left ventricular ejection time was related to an increase in stroke volume following greater ventricular filling.

The suggestion that ventricular compliance may be improved after propranolol is supported by the shortening of isovolumetric relaxation time (from 145 ±0·5 ms, to 122 ±10·3 ms), and the acceleration of the diastolic closure rate of the mitral echogram (47 ±4 mm/s, to 76 ±8 mm/s).

Isovolumetric relaxation time is related directly to the rate of ventricular relaxation and aortic pressure, and inversely to heart rate (Benchimol and Ellis, 1967). With the slowing of heart rate produced by propranolol, an increase in isovolumetric relaxation time might have been expected. As only a small, insignificant, change in blood pressure was found, shortening of isovolumetric relaxation time may reflect a better relaxation of the left ventricle. This is further supported by the concomitant acceleration of the diastolic closure rate of the mitral valve, for diastolic closure rate is related to the rate of ventricular filling (Wolfson, Ahmad, and Kerber, 1973; Layton *et al.*, 1973).

Echocardiography is an accepted method of measuring left ventricular diameters (Pombo *et al.*, 1971); therefore the increase in systolic and diastolic diameters induced by propranolol (Table) can be interpreted as a real dilatation of the ventricle.

TABLE *Results*

| *Case No.* | *HR* | | *LVETI* | |
|---|---|---|---|---|
| | *Control* | *Propranolol* | *Control* | *Propranolol* |
| 1 | 73 | 66 | 404 | 409 |
| 2 | 114 | 79 | 448 | 429 |
| 3 | 94 | 80 | 411 | 418 |
| 4 | 105 | 77 | 454 | 421 |
| 5 | 55 | 51 | 481 | 476 |
| 6 | 63 | 57 | 409 | 404 |
| 7 | 72 | 61 | 440 | 435 |
| 8 | 68 | — | 482 | — |
| 9 | 95 | 73 | 404 | 402 |
| 10 | 61 | 58 | 389 | 375 |
| 11 | 66 | 66 | 495 | 489 |
| 12 | 68 | — | 414 | — |
| 13 | 65 | — | 417 | — |
| 14 | 74 | 66 | 497 | 402 |
| 15 | 90 | — | 415 | — |
| 16 | 80 | 69 | 382 | 362 |
| 17 | 104 | 69 | 431 | — |
| Mean | 79 | 67 | 428 | 419 |
| SD | 18 | 9 | 33 | 37 |
| P value | | <0·005 | | <0·05 |

| *Parameters* | *Control ± SD* | *Propranolol* | |
|---|---|---|---|
| HR | 79 ±18 | 67 ±9 | (P < 0·005) |
| LVETI (ms) | 428 ±33 | 419 ±37 | (P < 0·05) |
| IRT (ms) | 145 ±9·5 | 122 ±10·3 | (P < 0·01) |
| DCR (mm/s) | 47 ±4 | 76 ±8 | (P < 0·001) |
| LVSD (cm) | 3·4 ±8 | 3·7 ±8 | (P < 0·05) |
| LVDD (cm) | 4·2 ±8 | 4·7 ±9 | (P < 0·05) |

HR: heart rate; LVETI: left ventricular ejection time index; IRT: isovolumic relaxation time; DCR: diastolic closure rate; LVSD: left ventricular systolic diameter; LVDD: left ventricular diastolic diameter.

The combination of ventricular dilatation, shortening of isovolumetric relaxation time, and acceleration of the diastolic closure rate of the mitral valve, may thus very well represent an improvement of ventricular compliance.

This explanation is in agreement with other observations from acute studies with practolol in HOCM (Webb-Peploe *et al.*, 1971), where the possibility of improved compliance was also suggested.

The resulting studies, therefore, indicate that non-invasive methods are capable of detecting haemodynamic changes produced by acute administration of propranolol, and that these changes suggest improved ventricular compliance.

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# Diazepam in acute myocardial infarction
## *Clinical effects and effects on catecholamines, free fatty acids, and cortisol*

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*Diazepam is a valuable drug in cases of acute myocardial infarction. The 10 mg intravenous loading dose and the subsequent 15 mg oral dose of diazepam administered three times daily produced safe, pleasant sedation, and reduced the need for analgesics. A much reduced excretion of catecholamines was recorded. It is presumed that diazepam causes a lower stress reaction, which is beneficial in diminishing the incidence of malignant arrhythmias and preventing the existing myocardial injury from spreading.*

Acute myocardial infarction represents a stress situation regularly accompanied by raised plasma concentrations of catecholamines, free fatty acids, and cortisol (Vetter *et al.,* 1974), which are among the factors held responsible for the occurrence of such serious complications as malignant arrhythmias, left ventricular failure, and cardiogenic shock (Jewitt *et al.,* 1969). Since the changes are also influenced to a great extent by emotional stress produced by pain and anxiety, a study was performed to measure the effect of sedation in the early phase of myocardial infarction. Diazepam was chosen for this purpose, as we have previously shown that this drug produces safe sedation, with no adverse respiratory or circulatory reactions. Oral and intravenous administration of diazepam was found to be superior to intramuscular injection (Hillestad *et al.,* 1974a); Hillestad, Hansen, and Melsom, 1974b).

This report describes the clinical effects of diazepam in myocardial infarction on the incidence of malignant arrhythmias, size of infarct, and sedation, and its effect on catecholamines, free fatty acids, and cortisol.

### Subjects and methods

Thirty-eight male patients aged 35 to 70 with proven acute myocardial infarction (admission less than 24 hours from the onset of pain) were diagnosed by means of WHO electrocardiographic criteria and by elevation of plasma aspartate aminotransferase (AST) levels. On admission the patients were randomly divided into a diazepam group and a control group, which later proved to be fairly comparable (Table 1). Patients who had previously been taking drugs that might influence the values (diazepam and diazepam-related compounds, corticoids, ataractics, and methyldopa) were not included in the trial, neither were patients with serious complicating diseases (renal failure, liver cirrhosis) that might interfere with the metabolism of diazepam. Patients who were in cardiogenic shock or in pulmonary oedema on admission were also excluded from the trial.

On admission patients in the diazepam group immediately received 10 mg diazepam (Stesolid) intravenously. One hour later they received an oral dose of 15 mg diazepam and this dose was repeated every 8 hours for three days. Blood samples for determination of plasma-cortisol concentrations (Mattingly, 1962) and free fatty acids (Dole, 1956)

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TABLE 1 *Clinical data of 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls)*

| | | *Diazepam group* | *Control group* |
|---|---|---|---|
| Mean age (y) | | 56 ± 6*<br>(range: 47–69) | 57 ± 7*<br>(range: 46–67) |
| Duration of pain before admission (no. of patients) | 0– 3 h | 9 | 5 |
| | 3– 6 h | 4 | 7 |
| | 7– 24h | 6 | 7 |
| Mean duration of pain before admission (h) | | 6·5 | 6·6 |
| *No. of patients with:* | | | |
| No previous illness | | 9 | 6 |
| Coronary heart disease | | 7 | 10 |
| Hypertension | | 3 | 1 |
| Obliterative atherosclerosis | | 0 | 2 |
| Mean maximum plasma aspartate aminotransferase (AST) (IU) | | 410 | 514 |
| Localization of infarct (no. of patients) | Anterior | 10 | 6 |
| | Diaphragmatic | 9 | 10 |
| | Posterior | 0 | 3 |

*Standard deviation.

were drawn on hospital admission, and thereafter every 12 or 24 hours for 72 hours. In addition, because of the rapid lowering of free fatty acids reported after acute myocardial infarction (Vetter *et al.*, 1974), blood samples were drawn for estimation 4 hours after admission.

The urinary output was collected over 24 hours for each of three consecutive days. Ten ml 10 per cent hydrochloric acid solution were added to the samples from which, after thorough mixing, 100 ml were withdrawn and deep-frozen for later determination of adrenaline, noradrenaline, and dopamine concentrations (Takahashi and Gjessing, 1972).

All patients were treated in a 6-bed intensive coronary care unit. This unit was connected to a 6-channel central oscilloscope which was placed in a separate room. The oscilloscope was constantly supervised by a trained nurse and all arrhythmias seen on the oscilloscope were recorded.

The patients were observed several times a day, and their mental state was rated according to the criteria listed in Table 2. Particular attention was paid to signs of diazepam intoxication, such as ataxia, confusion, and euphoria. The need for analgesics was registered as numbers of injections given, either 10 mg morphine or equivalent doses of similar drugs. Blood samples for determination of concentrations of diazepam and its metabolite, N-desmethyldiazepam, were drawn on hospital admission, and 4, 24, 48, and 72 hours after admission (Arnold, 1975). Plasma aspartate aminotransferase (AST) levels were determined on admission, and several times during the next 2 weeks.

The statistical analysis was done by the $\chi^2$-test and Wilcoxon's non-parametric rank test.

TABLE 2 *Mental state and need for analgesics in 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)*

| | *Diazepam group* | *Control group* |
|---|---|---|
| No signs of unwanted psychical reactions | 15 | 7 |
| Obvious signs of unrest and anxiety | 3 | 6 |
| Severe psychical reactions | 1 | 6 |
| Daily need for analgesics* | 3·7 | 5·0 |

*Number of injections, 10 mg morphine ore quivalent doses of similar drugs.

## Results

It appears from Fig. 1 that administration of diazepam as described caused a distinct accumulation of diazepam and its metabolite, N-desmethyldiazepam, and the same basic pattern was seen as already discussed by Hillestad *et al.*, 1974b). Continued diazepam treatment had a conspicuously beneficial effect on these patients as compared with the control group (Table 2). It reduced signs of unrest and anxiety ($P < 0{\cdot}01$). Psychoemotional disturbances were seen in the diazepam group only during the first 24 hours of the trial when the serum diazepam concentrations were below 250 ng/ml. At the end of the trial, mean diazepam concentrations of 510 ±215 ml (SD), and N-desmethyldiazepam concentrations of 281 ±110 ng/ml (SD) were determined. At this time about 70 per cent of the patients in the diazepam group had no memory of the first 24 hours in the coronary unit.

Very few adverse reactions were observed after

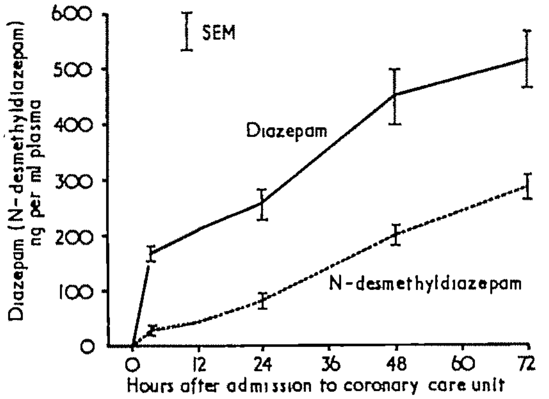

FIG. 1 *Mean plasma concentrations of diazepam and N-desmethyldiazepam in 19 patients with acute myocardial infarction treated with diazepam. (A loading dose of 10 mg i.v., followed by a 15 mg oral dose three times daily for three days.)*

TABLE 3 *Incidence of severe cardiac arrhythmias requiring treatment amongst 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)*

| | *Diazepam group* | *Control group* |
|---|---|---|
| No. of patients requiring treatment | 10 | 9 |
| Supraventricular arrhythmias | 8 | 5 |
| Ventricular ectopic beats (more than 6/min) | 6 | 5 |
| Third degree heart block | 0 | 1 |
| Ventricular tachycardia | 0 | 2 |
| Ventricular fibrillation | 0 | 1 |

diazepam administration. Some patients showed signs of slight ataxia, and a 69-year-old patient became confused and agitated when the serum concentrations of diazepam and N-desmethyldiazepam were 248 ng/ml and 61 ng/ml, respectively. These adverse reactions quickly abated and disappeared 12 hours after diazepam was discontinued. Otherwise, no adverse reactions were seen—in particular no haemodynamic effects.

Fewer analgesics were needed by patients in the diazepam group as compared with the patients of the control group (Table 2). In comparison with the control group the diazepam group had a lower mean aspartate aminotransferase (AST) level (Fig. 2) and a lower mean maximum AST value (Table 1), the differences, however, being statistically insignificant (P >0·10).

Malignant arrhythmias (ventricular tachycardia, third degree heart block, ventricular fibrillation) were seen only in the control group (Table 3). In the diazepam group, ventricular ectopic beats (more than 6 per minute) occurred only during the initial 12 hours after hospital admission (6 patients), whereas this arrhythmia was observed throughout the whole trial period in the control group (5 patients). No difference was seen between the groups in the incidence of heart failure, hypotension, and cardiogenic shock.

In the diazepam group no patients died during their stay in hospital, whereas in the control group one patient died 28 days after admission.

Patients treated with diazepam slept during most of the trial period, but could easily be awakened.

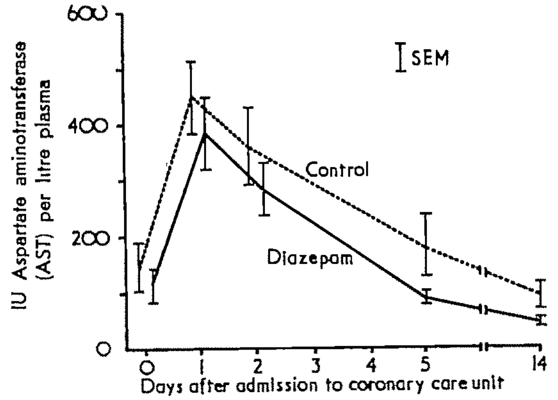

FIG. 2 *Mean plasma aspartate aminotransferase (AST) levels in 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls).*

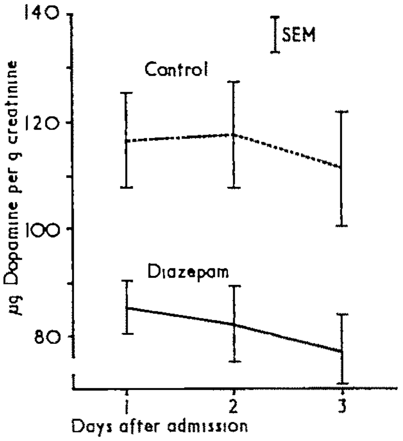

FIG. 3 *Mean dopamine excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 88 ±22 µg/g creatinine.*

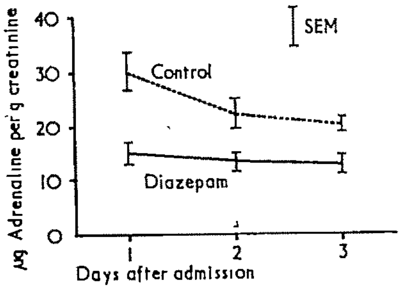

FIG. 4 *Mean adrenaline excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 6·1 ±1·8 µg/g creatinine.*

On interview, they expressed feelings of pleasant relaxation and were less concerned about their disease and the future than the patients in the control group.

The administration of diazepam produced a striking effect on the urinary excretion of catecholamines: a high urinary dopamine excretion was seen in the control group, but in the diazepam group it was within the normal range, and the difference between the two groups was highly significant (P < 0·01) (Fig. 3).

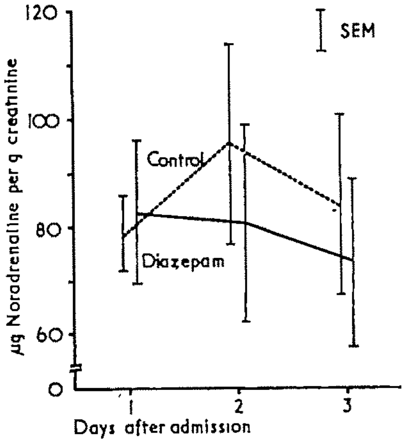

FIG. 5 *Mean noradrenaline excretion per day in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 20·5 ±9 µg/g creatinine.*

TABLE 4 *Incidence of heart failure, hypotension, and cardiogenic shock among 38 patients with acute myocardial infarction (19 patients treated with diazepam, and 19 controls)*

| | *No. of patients* | |
|---|---|---|
| | *Diazepam group* | *Control group* |
| Signs of pulmonary congestion on consultation | 3 | 4 |
| Pulmonary congestion in addition to peripheral oedema and/or gallop rhythm of heart | 2 | 3 |
| Pulmonary oedema | 0 | 1 |
| Hypotension | 3 | 3 |
| Cardiogenic shock | 2 | 1 |
| Died | 0 | 1 |

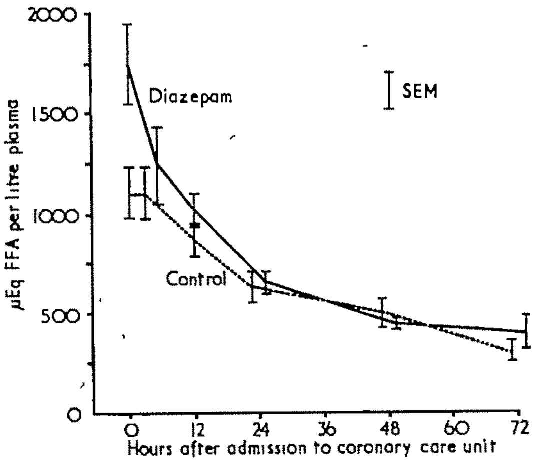

FIG. 6 *Mean plasma free fatty acid concentrations in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 400 to 800 µEq/l.*

In both groups the urinary adrenaline concentration was much above normal (Fig. 4). However, diazepam administration caused a significant reduction in adrenaline excretion (P < 0·001). The urinary noradrenaline concentration exceeded the normal value about fourfold, but no significant reduction (P >0·10) in the excretion of this substance was observed after diazepam administration (Fig. 5). There seems to be an extreme individual variation in the noradrenaline excretion as compared with excretion of adrenaline and dopamine.

On admission, the mean plasma free fatty acid concentrations in both groups were considerably increased, the diazepam group having the highest level (Fig. 6). After diazepam administration, the free fatty acid concentrations of the diazepam group initially decreased more rapidly than those of the control group. After 4 hours, there was no difference between the control group and the diazepam group,

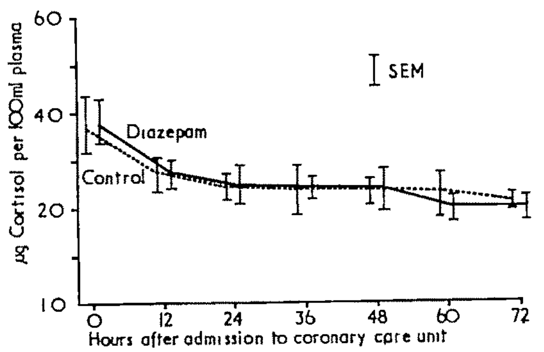

FIG. 7 *Mean plasma-cortisol concentrations in 38 patients with acute myocardial infarction (19 patients treated with diazepam and 19 controls). Normal range: 6·3 to 30·0 μg/100 ml.*

and after 24 hours, the values were within normal limits in both groups.

Diazepam administration did not affect the plasma-cortisol concentrations (Fig. 7). On admission, increased mean values were determined in both groups, showing a rapid decline during the first 12 hours and decreasing to normal range within the next 72 hours. No diurnal variation of plasma cortisol concentrations was seen during the trial.

## Discussion

In most cases, acute myocardial infarction gives rise to serious anxiety (Hackett, Cassem, and Wishnie, 1969). Pain will, in any circumstances, increase every patient's anxiety reactions. The diazepam dosage used in this study provided patients in a serious condition with safe sedation, yet negligible adverse reactions on physical and mental functions.

Previous studies have suggested that orally administered diazepam proves less effective than intravenously administered diazepam, but significantly more effective than intramuscularly administered diazepam (Hillestad *et al.,* 1974a, b). A good correlation was seen between the clinical effect (sedation) and the serum concentration level. Using diazepam as the sedative in myocardial infarction, it was found appropriate, therefore, to initiate treatment with an intravenous injection of the drug (a loading dose) followed by oral diazepam administration.

The clinical effects of the main metabolite, N-desmethyldiazepam, have not yet been completely assessed, but apparently it does not possess any potency as a sedative (Hillestad *et al.,* 1974a, b).

With the exception of a few days' delay for N-desmethyldiazepam, the accumulation of diazepam and N-desmethyldiazepam occurs mainly during the first week, after which a steady state between cumulation and elimination is maintained. To achieve better sedation a higher loading dose of diazepam should be given initially, and the subsequent oral doses should be reduced gradually to maintain the serum diazepam concentration below 500 ng/ml (Hillestad *et al.,* 1974a, b).

The amnesia produced by the diazepam treatment may be of special value in attenuating later psychoemotional problems, such as nightmares and cardiac neurosis. Diazepam is reported to be without analgesic effect, so that the reduced need for analgesics during the diazepam treatment is probably the result of an increased tolerance to pain (Bepko, Lowe, and Waxman, 1965). This observation is important, because administration of strong analgesics may suppress respiration, thus causing associated undesirable metabolic effects.

The findings of this study, viz. increased urinary excretion of catecholamines and high plasma free fatty acids and plasma cortisol levels, clearly show that acute myocardial infarction is a stress situation. The well-known correlation between plasma and urinary concentration of catecholamines (Fluck, 1972; Videbaek, Christensen, and Sterndorff 1972) makes it probable that using diazepam to treat patients with acute myocardial infarction caused a decreased plasma level of catecholamines. This conclusion may be of considerable importance, since increased plasma levels of catecholamines may cause ventricular arrhythmias and cardiogenic shock (Jewitt *et al.,* 1969; Siggers, Salter, and Fluck, 1971), and potentiate platelet aggregation (Ardlie, Glew, and Schwartz, 1966).

Adrenaline seems to be more connected with stress than does noradrenaline (Edmondson, Roscoe, and Vickers, 1972; Fluck, 1972). This may explain the lack of effect of diazepam treatment on the noradrenaline excretion.

We believe, despite the fact that continuous 24-hour recording tapes were not used, that serious ventricular arrhythmias did not remain undiagnosed. Our observation that diazepam seems to diminish the incidence of ventricular arrhythmias is in accordance with previous publications (Muenster *et al.,* 1967; Van Loon, 1968; Papp, 1969; Cristea, Coeugniet, and Dobrescu, 1970). This diminution may be the result of the decreased plasma catecholamine level, though the anti-arrhythmic effect of diazepam should be borne in mind.

An increase in the number of incidents of arrhythmias may be the consequence of high plasma free fatty acid levels (Oliver, Kurien, and Greenwood, 1968; Rutenberg, Pamintuan, and

Soloff, 1969), and it has been shown that the myocardial oxygen requirement is intensified by free fatty acids. The advantage of the rapid decline in raised free fatty acid levels after diazepam treatment is, therefore, notable.

The diazepam group and the control group were comparable in age distribution and clinical data (Table 1), and the average duration of pain before admission was also similar. However, among the very early admissions, i.e. less than 3 hours' duration of pain, 9 patients were found in the diazepam group and only 5 patients in the control group. The majority of very early cases in the diazepam group may explain the higher initial concentration of free fatty acids in this group. On the other hand, for the same reason a higher incidence of ventricular arrhythmias would be expected in the diazepam group, since the incidence of ventricular arrhythmias is highest in the early stage of myocardial infarction, but this was not seen in the present study.

Previous investigations indicate that the adrenocortical response in myocardial infarction is influenced by the amount of myocardial injury and not only by the stress reaction (Bailey, Abernethy, and Beaven, 1967); Logan and Murdoch, 1966; Chopra *et al.*, 1972; Vetter *et al.*, 1974). This observation may explain the lack of effect of diazepam on the increased cortisol level.

Although the difference in the plasma aspartate aminotransferase levels between the control group and the diazepam group is insignificant, this may suggest another beneficial effect of the drug. It has been shown that diazepam produces coronary vasodilatation in dogs (Abel, Reis, and Staroscik, 1970), and the coronary dilating effect of diazepam in patients with and without coronary heart disease was reported by Ikram, Rubin, and Jewkes (1973).

We conclude that the serious anxiety reactions seen during the initial phase of acute myocardial infarction can be controlled safely by means of diazepam. In addition, administration of diazepam might reduce both the incidence of malignant arrhythmias and the extension of existing injury.

The present study also shows that diazepam may serve to counteract the occurrence of deleterious hormonal imbalance during myocardial infarction.

Seventy-two hours after admission, a reduced daily diazepam dose of 15 mg, or less, is recommended considering the accumulation of diazepam as shown in Fig. 1. The dosage of diazepam has to be adjusted when administered to patients previously treated with anxiolytic agents. It should also be remembered that old patients often show a reduced tolerance to diazepam.

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# Significance of angina pectoris in aortic valve stenosis

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*Of 60 patients aged 45 to 66 years with aortic valve stenosis, 28 (47 per cent) had angina pectoris. Significant coronary arterial obstruction was shown by selective coronary cineangiography in 14 of them. Systolic pressure gradients across the aortic valve were lower in patients with angina than in those without. In those with angina, systolic gradients were higher in those with normal coronary arteriograms than in those with demonstrable coronary arterial disease.*

*Aortic valve replacement relieved the angina in all patients who had normal coronary arteriograms. When valve replacement was combined with coronary bypass grafting in those with coronary arterial disease, surgical mortality was higher and symptomatic relief less predictable.*

*Incapacitating angina in patients with aortic stenosis was nearly always associated with significant coronary disease. In those with less severe angina it was impossible to predict the state of the coronary arteries. Two patients, who did not have angina and who did not undergo coronary arteriography, died after aortic valve replacement and were found at necropsy to have unsuspected severe coronary disease. We, therefore, suggest that coronary arteriography should be carried out in all patients over the age of 40 years in whom surgery is being considered for aortic stenosis.*

Angina pectoris is a common symptom of aortic valve stenosis (Lewes, 1951; Mitchell *et al.*, 1954; Wood, 1958; Baker and Somerville, 1959; Basta *et al.*, 1975) and may occur in the absence of coronary artery disease (Linhart *et al.*, 1968; Hurst and Logue, 1970; Heulin *et al.*, 1973; Basta *et al.*, 1975). It is probably caused by ischaemia of a hypertrophic left ventricle which is subject to an excessive work load (Bonchek, Anderson, and Rösch, 1973). Coronary arteriography shows, however, that many such patients have significant coronary arterial obstruction (Loop *et al.*, 1972; Bonchek *et al.*, 1973; Berndt *et al.*, 1974; Basta *et al.*, 1973, 1975). This has a new importance now that coronary artery bypass grafting can be undertaken in addition to aortic valve replacement (Flemma *et al.*, 1971; Loop *et al.*, 1972; Anderson *et al.*, 1973; Berndt *et al.*, 1974). We, therefore, studied a series of patients with aortic valve stenosis who had angina pectoris, in order to assess the role of coronary artery disease in causing this symptom.

## Patients and methods

We investigated 73 consecutive adult patients with dominant aortic stenosis during the 25 months ending in January 1975. There were 53 men and 20 women and their ages ranged from 20 to 71 years. They were questioned regarding any history of chest pain. Angina pectoris was deemed to be present if they suffered from episodic retrosternal or praecordial pain with or without radiation to the neck, shoulders, or arms, which was brought on by effort, emotional stress, or exposure to cold, and relieved by rest or nitroglycerin. The severity of angina was graded as follows: grade 1—angina only with severe exertion; grade 2—angina with ordinary activity, emotional stress, or exposure to cold; grade 3—angina at rest, as well as with exertion or stress.

Risk factors such as family history of ischaemic heart disease, hypertension, excessive smoking, diabetes mellitus, obesity, and hyperlipidaemia were assessed in all those who had angina pectoris.

We judged the severity of the aortic stenosis from the peak systolic pressure gradient across the aortic valve. All cases had a gradient of more than 10 mmHg (1·3 kPa). Patients with significant aortic

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TABLE 1 *Comparison of 60 patients aged 45 to 66 years with and without angina pectoris*

| | | *Male* | *Female* | *Total* | *Mean age (y)* |
|---|---|---|---|---|---|
| No angina | | 24 | 8 | 32 | 54·2 |
| Angina pectoris | Grade 1 | 6 | 5 | 11 | |
| | Grade 2 | 8 | 1 | 9 | |
| | Grade 3 | 6 | 2 | 8 | |
| All | | 20 | 8 | 28 | 58·0 |

regurgitation or mitral valve disease were excluded from the study.

Selective coronary cineangiography was accomplished with either Sones or Judkins catheters in all patients with angina pectoris. Significant coronary artery disease was judged to be present when there was a narrowing of more than 60 per cent of one or more of the main coronary vessels.

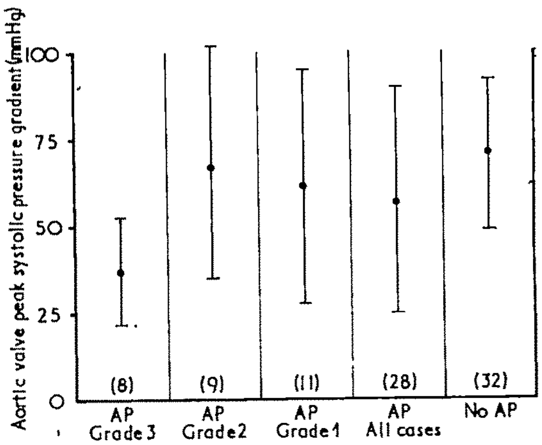

FIG. 1 *Aortic valve pressure gradient according to presence and severity of angina*

## Results

Of the 73 patients, 28 had angina pectoris. Their ages ranged from 45 to 66 years. They were compared with the 32 patients in the same age range, who had aortic stenosis but not angina pectoris, the other 13 being excluded from further consideration. The two groups were very similar as regards age and sex (Table 1). Of the 28 patients with cardiac pain, 11 had grade 1 angina pectoris, 9 grade 2, and 8 grade 3.

The mean of the peak systolic pressure gradients across the aortic valve was distinctly lower in those with angina pectoris than in those without (Table 2) (Fig. 1). Thus in the former group the range was 10 to 125 mmHg (1·3 to 16·6 kPa), with a mean of 56·9 mmHg (7·6 kPa), compared with 10 to 180 mmHg (1·3 to 23·9 kPa), with a mean of 70·3 mmHg (9·3 kPa) in the latter group of patients. In the 8 patients with severe (grade 3) angina the peak systolic pressure gradient was lowest of all (37·5 mmHg (5·0 kPa)) with a range of 10 to 55 mmHg (1·3 to 7·3 kPa). This was significantly lower than the gradient in those without angina (P<0·001).

TABLE 2 *Average peak systolic pressure gradients in relation to degree of angina pectoris*

| | | *No. of cases* | *Peak gradient (mmHg)** |
|---|---|---|---|
| Angina pectoris | Grade 3 | 8 | 37·5 (±15·6)* |
| | Grade 2 | 9 | 68·3 (±33·9) |
| | Grade 1 | 11 | 61·8 (±33·0) |
| | All | 28 | 56·9 (±32·1)† |
| No angina | | 32 | 70·3 (±21·4)*† |

*The difference between the pressure gradient in patients with grade 3 angina and in those with no angina is highly significant (P<0·001).

†The difference between the pressure gradient in all those with angina and in those without is not statistically significant.

*Conversion from Traditional Units to SI Units:* 1 mmHg≈0·133 kPa.

Coronary arteriography (Table 3) showed significant coronary artery disease in 14 of the 28 patients with angina, while in the other 14 the coronary arteries were considered normal. When the extent of the coronary disease was compared with the severity of angina pectoris we found that the more extensive the coronary artery disease, the more severe the angina pectoris tended to be. Thus 8 of the 11 patients with grade 1 angina had normal coronary arteriograms and the other 3 only single vessel disease; while of the 8 with grade 3 angina pectoris only 1 had a normal coronary arteriogram, whereas 5 of the other 7 had more than 1 coronary artery affected. These observations indicate that, while severe aortic stenosis often causes angina pectoris in the absence of demonstrable coronary artery disease, the angina tends to be mild or

TABLE 3 *Extent of coronary artery disease in patients with angina pectoris*

| | *Coronary arteriogram* | | | | |
|---|---|---|---|---|---|
| *Severity of angina pectoris** | *Normal* | *1-vessel disease* | *2-vessel disease* | *3-vessel disease* | *4-vessel disease* |
| Grade 1 (11) | 8 | 3 | 0 | 0 | 0 |
| Grade 2 (9) | 5 | 2 | 2 | 0 | 0 |
| Grade 3 (8) | 1 | 2 | 3 | 1 | 1 |
| Total (28) | 14 | 7 | 5 | 1 | 1 |

*Number of patients in parentheses.

TABLE 4 *Coronary arteriograms in severe and less severe angina pectoris*

| *Severity of angina pectoris* | *Normal coronary arteriogram* | *Abnormal coronary arteriogram* |
|---|---|---|
| Grade 1 and 2 | 13 | 7* |
| Grade 3 | 1 | 7* |

*The difference between patients with grade 3 angina and those with lesser degrees of angina is statistically significant (P<0·05).

moderate and rarely incapacitating. Severe angina pectoris in our patients was associated with significant coronary disease in all but one of 8 patients (Table 4). The histogram (Fig. 2), which includes data on all 28 patients with angina pectoris, indicates that those with normal coronary arteries had gradients of widely ranging severity, but when coronary disease was present there was a predominance of milder aortic stenosis as judged from the peak systolic pressure gradient. In the patients with angina pectoris, the aortic valve gradient in those who had normal coronary arteries averaged 70·7 mmHg (9·4 kPa) (±31·7) compared with 42·5 mmHg (5·7 kPa) (±25) in those with coronary artery disease (Fig. 3). The difference was most pronounced in patients in whom two or more of the coronary vessels were affected.

Assessment of risk factors in the patients with angina pectoris revealed that 20 of the 28 patients did in fact have evidence of one or more such factors (family history of ischaemic heart disease, hyperlipidaemia, hypertension, diabetes mellitus, excessive cigarette smoking) (Table 5). Of those with 2 or more risk factors, 7 out of 10 had coronary artery disease (70%) while among the 18 with one or no risk factors 7 had coronary artery disease (39%) and 11 had normal coronary arteriograms. Eleven out of 14 patients with coronary disease (79%) had one or more risk factors as compared with 9 out of 14 of those with normal coronary arteries (64%) (Table 5).

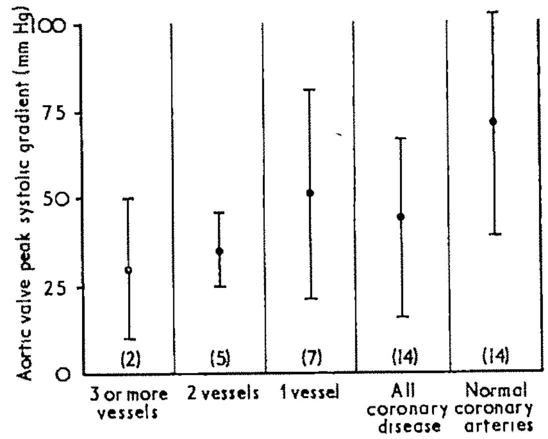

FIG. 3 *Aortic valve gradient in patients with angina according to the extent of coronary disease*

Of the 28 patients, 20 subsequently underwent surgical treatment (Table 6). In 12 of the 14 with normal coronary arteriograms, aortic valve replacement alone was carried out with an operative mortality of 1 (8%). One patient required a second operation some months later because of a paraprosthetic leak. In the remaining 10 patients angina pectoris was completely relieved. In 8 of 14 patients

TABLE 5 *Risk factors in relation to coronary arteriographic findings in 28 patients with angina pectoris*

| *Coronary arteriogram* | *Risk factors*<br>*None* | *One* | *Two* | *Three or more* | *Total with risk factors* |
|---|---|---|---|---|---|
| Normal (14) | 5 | 6 | 3 | – | 9 (64%) |
| Abnormal (14) | 3 | 4 | 5 | 2 | 11 (79%) |

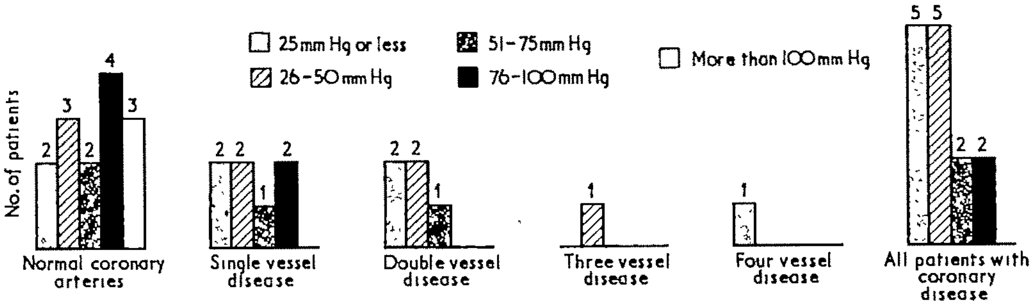

FIG. 2 *Aortic valve gradient in patients with angina in relation to the extent of coronary artery disease*

TABLE 6 *Results of surgery in the 60 middle-aged patients (aged 45 to 66 years)*

| | | Total | No. operated | Surgical mortality | Angina Abolished | Angina Improved | Angina Unchanged |
|---|---|---|---|---|---|---|---|
| Patients without angina | | 32 | 29* | 2 (7%) | — | — | — |
| Patients with angina | Normal coronary arteries | 14 | 12* | 1 (8%) | 11 | — | — |
| | Abnormal coronary arteries | 14 | 8† | 2 (25%) | 2 | 2 | 1 |

*Aortic valve replacement only.
†Aortic valve replacement plus saphenous vein bypass grafting.

with abnormal coronary arteriograms, one or more saphenous vein bypass grafts were inserted at the same time as the aortic valve was replaced. Two of these patients died shortly after operation (25% mortality). At necropsy, both these patients were shown to have extensive coronary atheroma with healed myocardial infarction. A further patient died suddenly a few weeks after operation from a myocardial infarction; the saphenous vein graft was shown to be patent at necropsy. Of the 5 surviving patients, angina was abolished in 2, improved in another 2, and unchanged in 1. Of the 8 patients who were not operated upon, 2 died within 12 months of investigation, one suddenly, and the other from congestive heart failure. Of the 32 patients who did not have angina, 29 underwent aortic valve replacement, with an operative mortality of 2 (7%). Both these patients were found at necropsy to have severe coronary artery disease with healed myocardial infarction which had not been suspected clinically or by electrocardiography.

## Discussion

Our findings confirm previous reports that angina pectoris is a common symptom of aortic stenosis. Thus, 47 per cent of the middle-aged patients in our series had angina pectoris. Heulin *et al.* (1973) found a similar incidence (44·4%) in a series of 52 cases of severe calcific aortic valve stenosis. The mean age of our patients with angina was 58 years, as compared with 54·2 years in patients without angina. Basta *et al.* (1975) reported similar mean ages of 57 and 54 years of their patients with and without angina, respectively.

An interesting finding was that the aortic valve gradients tended to be smaller in those patients with angina pectoris than in those without, particularly when the angina pectoris was severe. This seemed to be because of a greater prevalence of coronary artery disease in those with milder aortic stenosis. Berndt *et al.* (1974) had similar experience showing that the mean aortic systolic gradient was lower in patients with coronary artery disease than in those without. This implies that angina in those patients with significant coronary artery disease is more the result of the coronary disease than of the aortic stenosis. It is also possible that in some cases myocardial ischaemia and infarction resulting from coronary artery disease itself leads to a fall in the aortic valve gradient.

The reported incidence of coronary arterial obstruction in patients with combined aortic stenosis and angina is from just over 20 per cent to above 60 per cent (Linhart *et al.*, 1968; Berndt *et al.*, 1974; Parker, Jacob, and Seabra-Gomes, 1974; Basta *et al.*, 1975). The incidence in our series was 50 per cent (14 of 28 patients).

Basta *et al.* (1975) reported that all of 19 patients with aortic stenosis who did not have angina had normal coronary arteriograms. Others, however, have found a significant incidence of coronary arterial disease in this category of patients. Loop *et al.* (1972), in their series of patients with aortic or mitral valve disease, found abnormal coronary arteriograms in 28 per cent of cases who had no history of angina. More recently Harris *et al.* (1975) have found an incidence of 10·3 per cent in their series of patients with dominant aortic stenosis. Two of our patients who had no angina were subsequently found at necropsy to have severe coronary artery disease. We, therefore, agree with Bonchek *et al.* (1973) that coronary arteriography should be undertaken in all patients over the age of 40 in whom aortic valve replacement is being considered. This should not only provide guidance to the surgeon as to the need for coronary artery grafting in addition to the valve replacement but also should help in assessing the risk of operation.

We wish to thank Dr. J. Pilcher who was responsible for some of the patients and their investigations and Mr. W. G. Williams and Mr. J. A. Dyde who carried out the surgical treatment.

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# Calcific coronary embolization associated with cardiac valve replacement
## *Necropsy* x-*ray study*

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*The hearts of 14 patients dying early after replacement of a calcified aortic or mitral valve were examined for the presence of calcific coronary emboli. The incidence of embolization as shown by* x-*ray film was 92·9 per cent. The number of emboli in individual cases ranged from 4 to 119. Replacement of an aortic valve was associated with a more severe embolization than replacement of a mitral valve. The mechanisms of calcific embolization are discussed and preventive surgical measures suggested.*

A calcified aortic or mitral valve may be a source of systemic calcific embolization. This may occur spontaneously (Moragues, Bawell, and Shrader, 1950; Wigle, 1957; Holley *et al.*, 1963a), or after various intracardiac procedures, particularly operations on such valves (Glotzer, Shaw, and Scannell, 1962; Holley *et al.*, 1963b).

Several necropsy studies of cardiac valve replacement mention the finding of calcific coronary emboli; however, the true incidence and significance of this complication are unknown (Hudson, 1965, 1970; Morales, Fine, and Taber, 1967; Henson *et al.*, 1969; Colapinto and Silver, 1971; Roberts, Bulkley, and Morrow, 1973).

### Patients

During the period September 1973 to August 1975 there were 34 deaths following prosthetic heart valve replacement. We have examined the hearts of 14 patients who met the following criteria: (1) severe calcification of the diseased valve; (2) death in the first postoperative week.

Of the 14 patients, 12 were men and 2 were women; their ages ranged from 39 to 60 years (average 47). The aortic valve alone was replaced in 7 patients and the mitral valve alone in another 7. The valve was excised intact in 8 patients, and in several pieces in 6 (5 aortic, 1 mitral). The operations were performed under moderate body hypothermia and anoxic heart arrest induced by clamping the ascending aorta. Coronary arterial perfusion was not used.

### Methods

The heart was excised from the chest organs and the ventricles sliced at 1 to 1·5 cm intervals, beginning at the apex and stopping 2 to 3 cm from the atrioventricular valve rings. Depending on the heart size, 5 to 7 slices were obtained. The coronary arteries on the basal portion of the heart were opened longitudinally.

The formalin-fixed slices were *x*-rayed by Mammograf (Siemens) on a Mammoray T 1 film at focus size 0·6 mm, 28 kV and 200 to 250 mÅ, with a focus-film distance of 47 cm.

The site of the calcific particles was recorded on transparent paper, with the ventricular cross-sectional plane divided into 5 segments: anterior, lateral, posterior, the right ventricle, and the septum (Fig. 1). According to the greatest dimension, the particles were classified as small (<0·5 mm), medium-sized (0·5–1 mm), and large (>1 mm).

The nature of most of the particles was checked, either grossly, or histologically.

### Results

Gross calcific coronary embolus was found in 2 patients after aortic valve replacement, measuring

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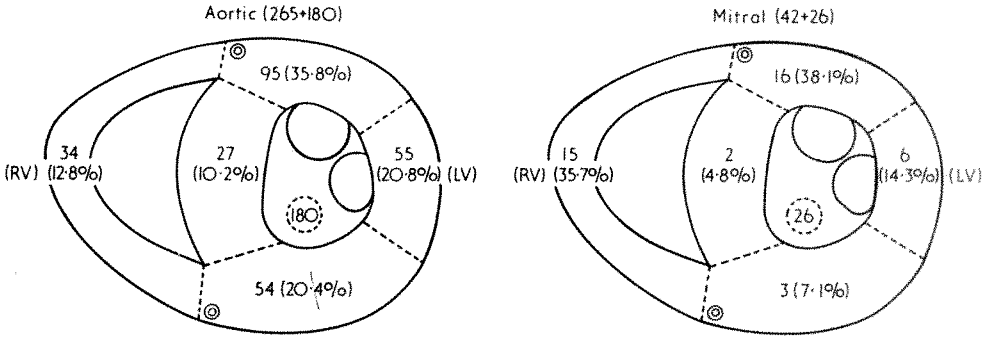

FIG. 1 *Distribution of the total 513 calcific particles (307 coronary emboli plus 206 intraventricular) in aortic vs. mitral valve replacement.*

respectively, 4 mm and 2·5 mm in greatest dimension. In one case the embolus was in the anterior descending artery and in the other in the posterior descending branch of the right coronary artery.

**Calcific coronary emboli** (Table 1, Fig. 2)

These were present in 13 of the 14 patients (93%). The number of emboli in individual cases ranged between 4 and 119. Of the total 307 emboli, 208 were small, 63 medium-sized, and 36 large. One hundred and twenty (39%) were lodged in the subepicardial arteries, and 187 (61%) in the intramyocardial branches.

There was no obvious difference in the number of emboli between the patients with the valve excised intact and those with the valve removed in several pieces.

**Calcific particles in left ventricular cavity** (Table 1, Fig. 3)

These were present in 12 patients, adjacent to the endocardium between the papillary muscles and the trabeculae. The number of particles in individual cases ranged between 1 and 47. Of the total 206 intraventricular particles, 168 were small, 29 medium-sized, and 9 large. The majority were on the posterolateral wall, between both papillary muscles. In most instances the number of particles was related to the number of coronary emboli.

**Aortic vs. mitral valve replacement** (Table 2, Fig. 1)

Both the emboli and the intraventricular particles were much more common in the aortic valve replacement, as shown in Table 2. There was also a different distribution of the emboli (Fig. 1); in

TABLE 1 *Calcific coronary emboli associated with cardiac valve replacement in 14 necropsy patients*

| *Case No.* | *Valve replaced* | *Calcific coronary emboli* | | | | *Calcific particles in LV cavity* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Small* | *Medium-sized* | *Large* | *Total* | *Small* | *Medium-sized* | *Large* | *Total* |
| 1 | Aortic | 25 | 13 | 2 | 40 | 20 | 5 | 0 | 25 |
| 2 | Mitral | 3 | 0 | 1 | 4 | 0 | 0 | 0 | 0 |
| 3 | Aortic | 22 | 6 | 3 | 31 | 31 | 5 | 2 | 38 |
| 4 | Aortic | 19 | 1 | 0 | 20 | 20 | 3 | 1 | 24 |
| 5 | Mitral | 7 | 0 | 0 | 7 | 5 | 4 | 0 | 9 |
| 6 | Mitral | 7 | 3 | 2 | 12 | 3 | 0 | 0 | 3 |
| 7 | Aortic | 74 | 27 | 18 | 119 | 17 | 0 | 0 | 17 |
| 8 | Aortic | 3 | 1 | 0 | 4 | 33 | 8 | 6 | 47 |
| 9 | Mitral | 7 | 2 | 1 | 10 | 7 | 2 | 0 | 9 |
| 10 | Mitral | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | Mitral | 3 | 1 | 0 | 4 | 4 | 0 | 0 | 4 |
| 12 | Aortic | 32 | 7 | 8 | 47 | 23 | 2 | 0 | 25 |
| 13 | Mitral | 3 | 2 | 0 | 5 | 1 | 0 | 0 | 1 |
| 14 | Aortic | 3 | 0 | 1 | 4 | 4 | 0 | 0 | 4 |
| Total | | 208 | 63 | 36 | 307 | 168 | 29 | 9 | 206 |

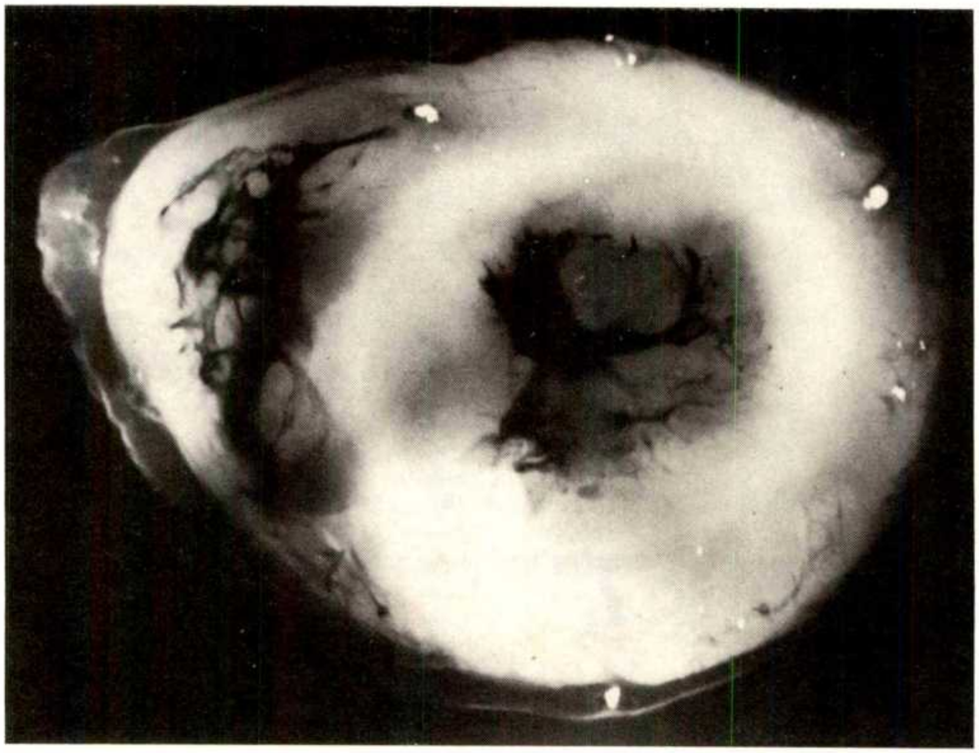

FIG. 2 *An x-ray picture of a midventricular slice of the heart of Case 7 shows numerous calcific coronary emboli both subepicardially and intramurally. The calcified aortic valve was removed in one piece 7 days before death. The postoperative course was dominated by features of low cardiac output syndrome with ischaemic changes on the electrocardiogram (×1.3).*

aortic valve replacement the left coronary artery appears to be more severely affected and the right coronary artery less so, when compared with the mitral valve.

Histological examination of the myocardium showed focal necroses in the left ventricle and the ventricular septum in each of the 10 patients who survived more than 1 day. These were extensive in 3 patients, all of whom had aortic valve replacement. In the one case with gross embolus in the posterior descending coronary branch a small myocardial infarction was found distal to the site of occlusion.

## Discussion

This study has shown that replacement of a calcified heart valve, and particularly of the aortic valve, is frequently associated with calcific coronary embolization. The aortic valve, compared with the mitral valve, is usually more heavily calcified and the calcium more often extends into the adjacent heart structures. During resection of such a valve, fragments of calcium fall into the left ventricular cavity. Those which get entrapped between the trabeculae may not be removed by the surgical toilet. After resumption of blood flow some of them are washed out to become systemic emboli. This is probably the basic mechanism of calcific coronary embolization. Thus, the pattern of embolization in mitral valve replacement (Fig. 1), in which this basic mechanism operates alone, may be regarded as reflecting the average distribution of the coronary blood flow.

In aortic valve replacement an additional mechanism is suggested by the more severe involvement of the anterior and lateral heart segments which are supplied by the left coronary artery (Fig. 1); during manipulation with the valve, fragments of calcium may fall directly into the coronary ostia, mainly into the left, which is widely exposed.

The *x*-ray method used in this study proved capable of detecting calcific particles as small as

TABLE 2 *Calcific coronary emboli associated with aortic vs. mitral valve replacement in 14 necropsy patients*

| | | Valve replaced | |
|---|---|---|---|
| | | *Aortic (7 cases)* | *Mitral (7 cases)* |
| Calcific coronary emboli | No. of patients affected | 7 | 6 |
| | Total no. of emboli | 265 (86·3%) | 42 (13·7%) |
| | No. of emboli in individual patients | 4–119 (av. 38) | 0–12 (av. 6) |
| Calcific particles in LV cavity | No. of patients affected | 7 | 5 |
| | Total no. of particles | 180 (87·4%) | 26 (12·6%) |
| | No. of particles in individual patients | 4–47 (av. 26) | 0–9 (av. 4) |

0·1 to 0·15 mm. It also allowed easy distinction of the fragments of calcium from the shell-like calcifications of atheromatous lesions.

Particles smaller than 0·1 mm are unlikely to be detected during histological examination except by chance. Nevertheless, in our previous study of 68 necropsy patients (Steiner, Křivková, and Procházka, 1975), the histological incidence of calcific coronary emboli from the calcific valves only was 24 per cent with isolated mitral valve replacement, 53 per cent with isolated aortic valve replacement, and 75 per cent with mitral plus aortic valve replacement. The true incidence and extent of calcific microembolization must, however, be much higher, as only 2 to 3 per cent of the total heart mass is taken for histology and from this the paraffin sections form approximately 1/200 to 1/300.

Examination of the hearts of patients dying at longer intervals after the operation (not included in this study) allowed us to follow the natural history of the emboli. Even several years after operation

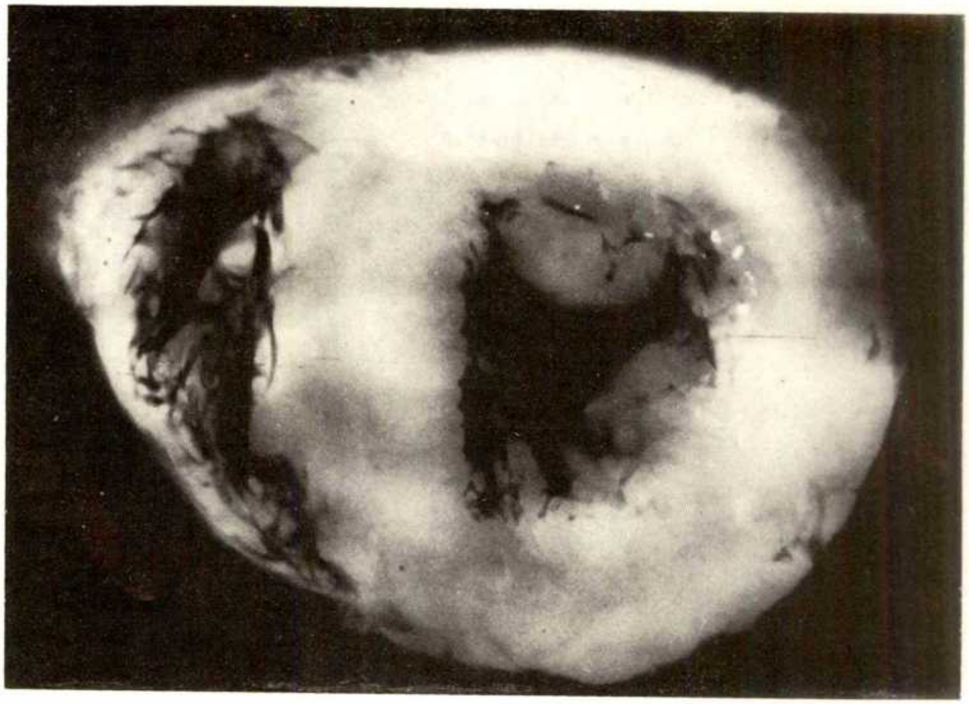

FIG. 3 *An x-ray picture of a midventricular slice of the heart of Case 8 shows calcific particles in the left ventricular cavity. Most particles are on the endocardium of the posterolateral wall between the papillary muscles. The calcified aortic valve was removed in 5 pieces. The patient died from diffuse hypoxic damage of the brain 5 days after operation.* (× 1·5.)

the calcific particles can be seen on *x*-ray film, both as coronary emboli and intraventricularly. Microscopically, they are completely covered by collagen, as a result of the intimal, or endocardial reaction. The embolus may occasionally be extruded from the artery and is found perivascularly.

It is difficult to assess the clinical importance of calcific coronary embolization as similar ischaemic myocardial lesions may also be seen with replacement of non-calcified valves. It was thought to be the prime cause of death in 2 patients and its role was seriously considered in an additional 3 who died with low cardiac output syndrome, which was otherwise unexplained by the necropsy.

As the coronary circulation receives approximately 4 per cent of the cardiac output, it may be presumed that a considerable number of the calcific particles from the left ventricle embolize to other organs, e.g. the brain and the kidneys.

The results of this study warrant the recommendation of certain preventive surgical measures:

(1) Occlusion of the coronary ostia during manipulation of the aortic valve.

(2) Removal of the calcium extending into the valve ring and the surrounding structures.

(3) A thorough cleansing of the left ventricle and the aortic root before the circulation through the heart is restored.

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# Anatomical variants in aortic atresia
## *Potential candidates for ventriculoaortic reconstitution*

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*Aortic valve atresia is usually associated with severe hypoplasia of the left ventricle and mitral apparatus. Palliative procedures, including atrial septectomy, pulmonary artery—aorta anastomosis, and pulmonary artery banding, have been performed in some patients. However, because of the distinct underdevelopment of the left heart, the long-term prognosis must be guarded even in the survivors of these procedures.*

*Rarely, aortic valve atresia is found with adequate left heart chambers. Because very few of these patients are described, the clinical, angiocardiographic, and pathological findings in two patients are presented, with comments on palliation in the neonatal period, and the potential for ventriculoaortic reconstitution.*

Aortic valve atresia is usually associated with severe hypoplasia of the left ventricle and mitral apparatus (Lev, 1952). Survival for even a short time depends on patency of the ductus arteriosus and lack of significant restriction at the atrial septum (Noonan and Nadas, 1958; Saied and Folger, 1972). With medical therapy alone, the majority of patients with aortic atresia and hypoplasia of the left heart chambers are dead by 6 weeks of life (Noonan and Nadas, 1958; Watson and Rowe, 1962; Saied and Folger, 1972). Surgical palliation of less severe forms of the hypoplastic left heart syndrome has included atrial septectomy and construction of a pulmonary artery —aortic anastomosis, but only a few survivors of these procedures have been reported (Sinha *et al.,* 1968; Cayler, Smeloff, and Miller, 1970; Van Praagh *et al.,* 1971), and even in the survivors of these palliative procedures the long-term prognosis must be guarded. To our knowledge, no patient with aortic atresia has survived such palliative surgery, though this approach was suggested in 1967 (Keith, Rowe, and Vlad, 1967).

Rately, aortic valve atresia is found with adequate left heart chambers. However, very few of these patients are discussed (Rosenquist, Taylor, and Stark, 1974). In order to define this clinically important entity, the clinical and pathological findings in two such patients will be presented, with comments on palliation in the neonatal period, and the potential for ventriculoaortic reconstitution (Bernhard, Poirier, and LaFarge, 1975).

## Case reports

### Case 1

This 6-day-old female infant presented with signs of congestive heart failure and cyanosis.

Physical examination showed a mildly distressed, tachypnoeic (80/min) infant, with mild generalized cyanosis. All pulses were easily palpable. Systolic blood pressure in the arms was 90 mmHg (12·0 kPa) and in the legs 100 mmHg (13·3 kPa).

Cardiac examination revealed a biventricular impulse, single second sound, constant ejection click along the left sternal border, and a short ejection murmur. A gallop was audible at the left lower sternal border. The liver was palpable 3·0 cm below the right costal margin.

Chest *x*-ray film showed laevocardia, modest cardiac enlargement, and pulmonary overcirculation. Pulmonary oedema was not present. There was visceral situs solitus (Fig. 1).

The electrocardiogram showed sinus tachycardia, right axis deviation and right ventricular hypertrophy (Fig. 2).

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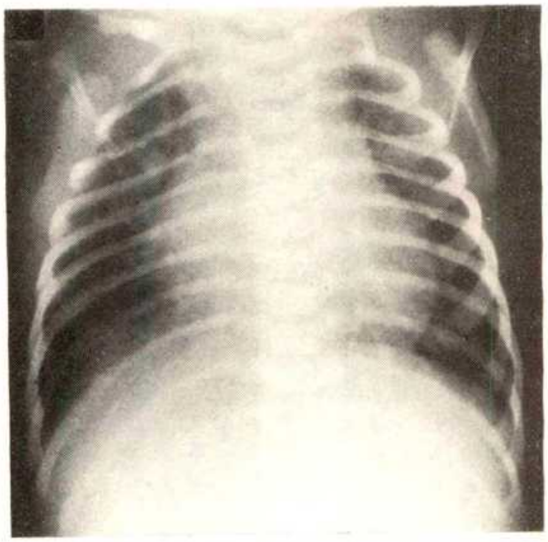

FIG. 1 *Case 1: Laevocardia and visceral situs solitus. The heart is modestly enlarged, and pulmonary overcirculation is evident.*

Echocardiography suggested a normal to large right ventricle, large left atrium and left ventricle, and one large anterior arterial root. These findings were interpreted as consistent with truncus arteriosus. Both tricuspid and mitral valves appeared normal, and there was a ventricular septum.

Diagnostic cardiac catheterization and angiocardiography were performed shortly after admission. The haemodynamic results are summarized in the Table. Left ventricular angiocardiography showed a normal-sized morphological left ventricle, high, possibly supracristal ventricular septal defect, and opacification of an anteriorly placed pulmonary artery (Fig. 3a, b). The ascending aorta did not opacify from this injection. An angiogram in the main pulmonary artery showed dilated pulmonary arteries, right-to-left shunting of the ductus arteriosus, with opacification of the descending

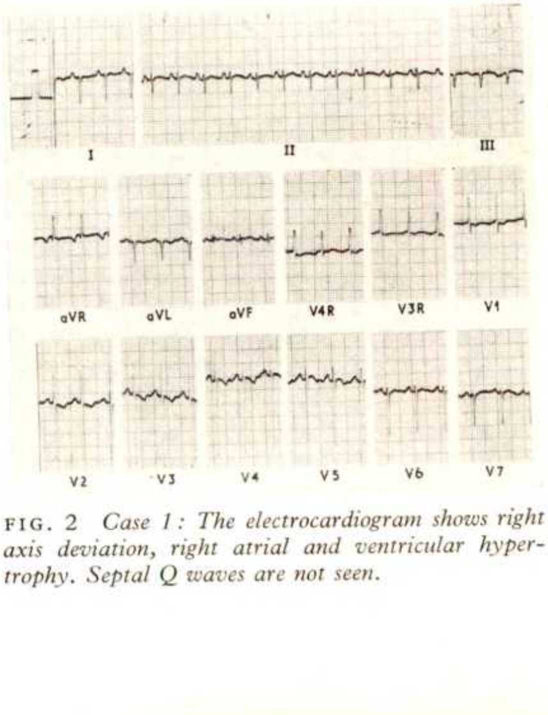

FIG. 2 *Case 1: The electrocardiogram shows right axis deviation, right atrial and ventricular hypertrophy. Septal Q waves are not seen.*

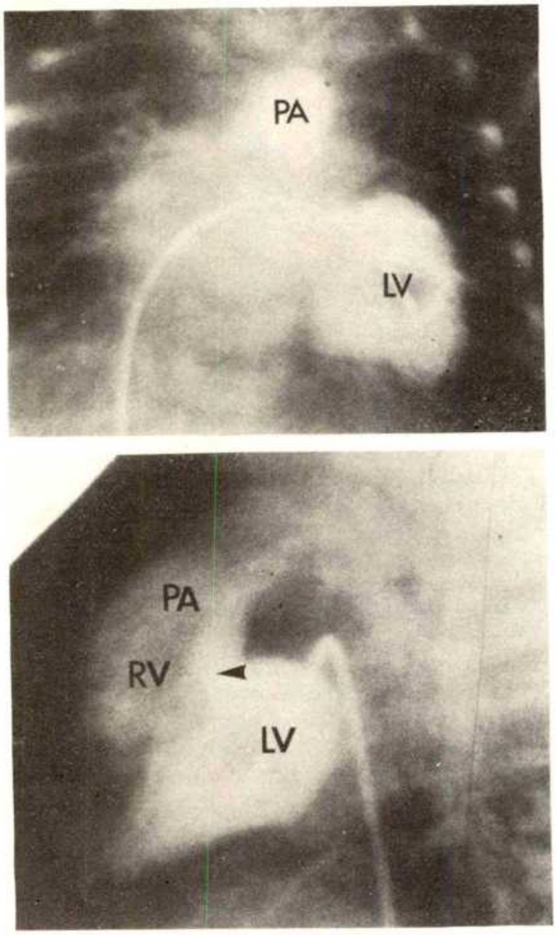

FIG. 3a, b *Case 1: Frames from left ventricular cineangiocardiogram in anteroposterior and lateral projection. The venous catheter has been advanced from the inferior vena cava through an atrial communication into the left ventricle (LV). A normal-sized left ventricle (LV) is opacified, with visualization of an anterior pulmonary artery (PA). A ventricular septal defect (arrow) is seen with opacifications of the anterior right ventricle. The aortic arch and branchiocephalic vessels are not clearly seen.*

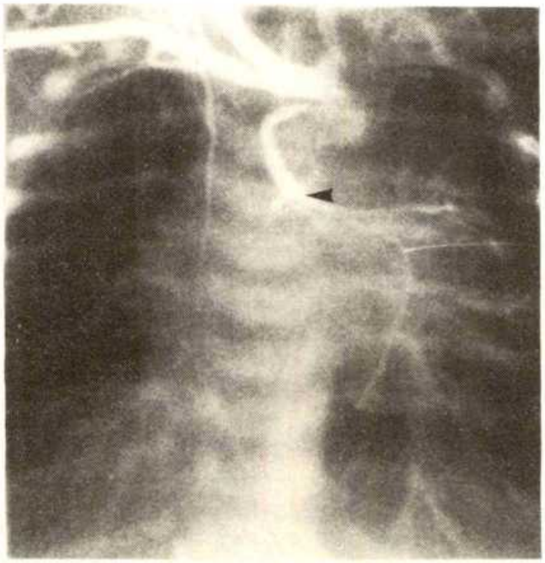

FIG. 4 *Case 1: Frame from an aortogram in the anteroposterior projection. A catheter has been advanced from the right axillary artery to the aorta. A diminutive ascending aorta (arrow) is visualized, with retrograde opacification of the coronary arteries.*

thoracic aorta, and retrograde filling of a diminutive ascending aorta. The pulmonary artery laevophase visualized pulmonary venous return, a normal left atrium, and normal left ventricle. Finally, using a right axillary artery approach, an ascending aortogram showed a diminutive ascending aorta with retrograde visualization of the coronary arteries (Fig. 4). Left ventricular volume measurements were calculated for two consecutive beats using the area–length method (Dodge *et al.*, 1960). The left ventricular end diastolic volume was 49 $cm^3/m^2$ and the left ventricular end systolic volume was 18 $cm^3/m^2$, giving an ejection fraction of 64 per cent.

TABLE *Haemodynamic data (Case 1)*

| *Site* | *$O_2$ saturation (%)* | *Pressure (mmHg)* |
|---|---|---|
| Superior vena cava | 67 | |
| Right atrium | 79 | Mean = 11 |
| Inferior vena cava | 68 | |
| Right ventricle | 85 | 80/10 |
| Main pulmonary artery | 86 | 85/50 (65) |
| Left atrium | 94 | Mean = 13 |
| Left ventricle | 92 | 90/12 |
| Descending aorta | 84 | 85/36 (50) |

*Conversion from traditional units to SI units:* 1 mmHg ≈ 0·133 kPa.

After the catheter procedure, a 6 mm Potts anastomosis was constructed, and bilateral pulmonary artery banding was performed. The procedure was well tolerated, and the infant was discharged much improved, two weeks after operation. Six months after operation, her growth and development were satisfactory and she was not admitted to hospital again.

### Case 2

This male infant presented at 3 days of age with mild congestive heart failure. Cardiac examination showed normal pulses, a single second heart sound, and a soft systolic murmur.

Chest *x*-ray film showed laevocardia, moderate cardiomegaly, and pulmonary over-circulation (Fig. 5).

The electrocardiogram was reported to show superior axis, right atrial and right ventricular hypertrophy (tracing is not available for reproduction).

Shortly after admission, the infant aspirated, sustained a cardiorespiratory arrest, and could not be resuscitated.

Pertinent necropsy findings were limited to the cardiovascular system. Laevocardia was present, and visceroatrial situs solitus, with the right-sided atrium receiving superior and inferior vena cava and coronary sinus. The morphological right ventricle

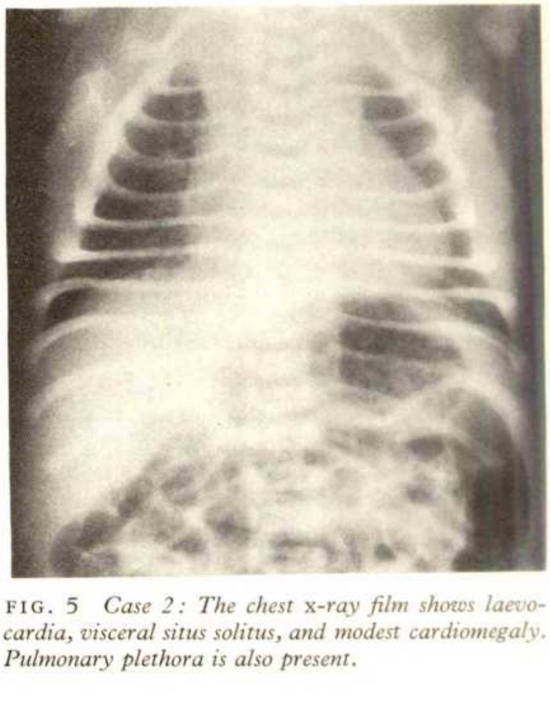

FIG. 5 *Case 2: The chest* x-*ray film shows laevocardia, visceral situs solitus, and modest cardiomegaly. Pulmonary plethora is also present.*

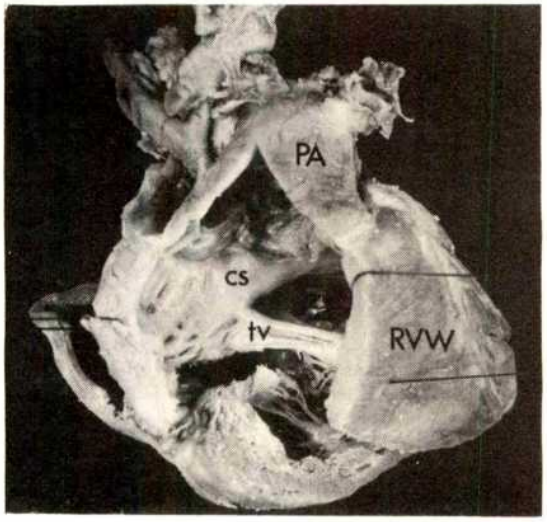

FIG. 6 *Case 2. Internal view of morphological right ventricle. The dilated pulmonary artery (PA) originates above the crista supraventricularis (cs), and the pulmonary valve above is separated from the tricuspid valve component (tv) below. The right ventricular wall (RVW) is thickened (7·0 mm).*

was right-sided and was hypertrophied and dilated (d-ventricular loop). A common atrioventricular valve was present, and there was considerable attachment of the common AV valve to the crest of the muscular ventricular septum. The subpulmonary conus was well developed, with semilunar atrioventricular valve discontinuity. The very large, dilated pulmonary artery originated above the subpulmonary conus (Fig. 6). The pulmonary valve was tricuspid. Pulmonary venous return to left atrium was normal. The left atrial chamber was of normal size. The mitral valve was grossly abnormal. The aortic leaflet of the mitral valve was cleft, and the distinct medial attachment of this leaflet of the mitral valve to the posterior edge of the grossly deficient ventricular septum was responsible for virtual subaortic atresia. The left ventricle measured 3·2 cm in vertical axis and appeared only slightly smaller than the grossly hypertrophied right ventricle (Fig. 7). The aortic valve was atretic and was formed of two, fused semilunar cusps. The diameter of the atretic aortic valve was 3·0 mm. The ascending aorta was diminutive (Fig. 8). The aortic arch was left-sided with normal brachiocephalic vessels. The ductus arteriosus was patent. In addition, there was evidence of aspiration, pneumonic, and hepatic congestion.

Final anatomical diagnoses: laevocardia, atrial situs solitus, d-ventricular loop, complete common atrioventricular canal, subaortic and aortic valve atresia secondary to anomalous attachment of mitral valve, persistent ductus arteriosus, and normal left atrium and left ventricle.

## Discussion

The recent reports of Bernhard and his colleagues lend impetus to the possibility that ventriculoaortic reconstitution may be afforded some select patients with aortic atresia (Bernhard *et al.*, 1975). They successfully bypassed extreme valve and supravalve aortic stenosis with associated hypoplasia of the aortic valve annulus in a 22-year-old patient with angina and syncope that had proved refractory to standard surgical intervention. In their patient, a valved conduit was positioned between the left ventricular apex and descending thoracic aorta. The patient was significantly improved by the operation and the laevophase of a postoperative biplane pulmonary arteriogram showed that the contrast was ejected through the prosthesis, with none passing through the patient's own aortic valve and hypoplastic outflow tract.

There is an alternative approach to the use of a

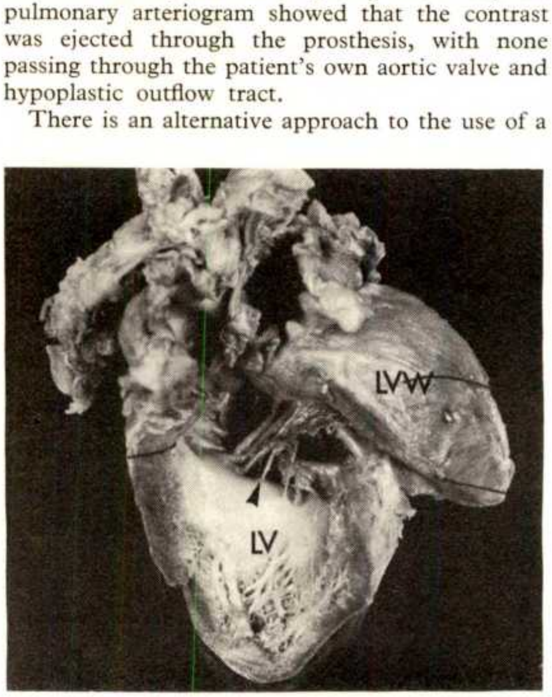

FIG. 7 *Case 2: Internal view of the left-sided morphological left ventricle. The left ventricle (LV) is of normal size. The large ventricular component of the complete AV canal is seen, and is not restrictive (arrow). The mitral valve has a cleft anterior leaflet, and extreme subaortic obstruction results from the abnormal medial attachment of the anterior leaflet of mitral valve. The left ventricular free wall (LVW) is of normal calibre.*

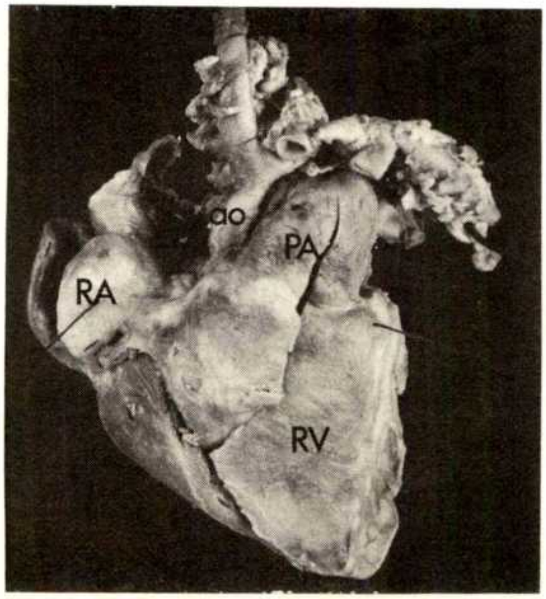

FIG. 8 *Case 2: External view of heart showing relation between pulmonary artery (PA) and ascending aorta (ao). The main pulmonary artery is anterior and is considerably larger than the ascending aorta. The diminutive ascending aorta (ao) originates posteriorly, inferiorly, and slightly to the left of the pulmonary artery. The relative size of the great arteries suggests the typical features of the hypoplastic left heart syndrome. with significant hypoplasia of left ventricle and mitral valve apparatus. The large right atrial appendage (RA) is also seen.*

ventriculo-aortic conduit. The ventricular septal defect could be patched into the pulmonary artery, providing left ventricular pulmonary artery continuity. The origins of the right and left branch pulmonary arteries could be divided from the main trunk, and right ventricular pulmonary artery integrity could be established by using a prosthetic bifurcation graft from right ventricle to branch pulmonary arteries. The ductus and Potts shunt would then provide continuity to the descending thoracic aorta. This hypothetical technique has the advantage that the patient's own semilunar (pulmonary) valve would then serve as the patient's systemic semilunar valve.

The presence of an adequate left ventricle, without associated endocardial fibroelastosis or mitral valve hypoplasia, is a most unusual departure from the usual pathological findings in the patient with aortic atresia (Lev, 1952; Noonan and Nadas, 1958; Saied and Folger, 1972; Sinha *et al.*, 1968; Kanjuh, Eliot, and Edwards, 1965). It is difficult to estimate the frequency of this association, but undoubtedly it is rare. Rosenquist *et al.* recently described an infant with aortic atresia, aortopulmonary fenestration, interrupted aortic arch, ventricular septal defect, and persistent ductus arteriosus. The left ventricle in their patient was 2·7 cm in length, and their comments and diagrams suggest that the left ventricle was of reasonable size (Rosenquist *et al.*, 1974).

A complete atrioventricular canal and aortic atresia with a diminutive ascending aorta are the pertinent pathological findings in Case 2. The subaortic area in this patient was extremely narrowed by abnormal insertion of the aortic leaflet of the mitral valve and by deposition of accessory endocardial cushion tissue. There are at present many reports describing the anomalous attachment of the mitral valve causing subaortic stenosis (Ferencz, 1957; Bjork, Hultquist, and Lodin, 1961; Sellers, Lillehei, and Edwards, 1964). As Edwards has previously stated: 'a variety of mitral valvular lesions may be responsible for subaortic stenosis. There is, however, a consistent association between the mitral valvular lesion of persistent common atrioventricular canal (so called endocardial cushion defect) and actual or potential subaortic stenosis' (Jue and Edwards, 1967). Coexistent aortic and mitral atresia have been associated with persistent common atrioventricular canal (Silberberg, 1965). But, unlike our second patient, there was apparently aplasia of the left ventricle in the patient described by Silberberg. Indeed, significant hypoplasia of the left ventricle seems to be the rule in patients with atrioventricular canal and subaortic atresia.

Differentiation of the patient with aortic atresia and adequate left ventricle from the patient with aortic atresia and diminutive left ventricle and mitral apparatus is probably not possible on clinical grounds alone. Survival in both depends on patency of the ductus arteriosus and with ductal restriction systemic and coronary perfusion will become inadequate, metabolic acidosis will become irrevocable, and shortly the patient will die. The electrocardiograms will probably not be helpful in distinguishing between the two. Even if good left ventricular voltage were present, this should not be interpreted as suggesting an adequate left ventricular cavity. Strong, Liebman, and Perrin (1970) described 4 patients with hypoplastic left heart syndrome and electrocardiographic evidence for left ventricular hypertrophy. Similarly, in the review by Noonan and Nadas (1958) of the hypoplastic left heart syndrome, 4 of 50 patients had left ventricular hypertrophy on electrocardiogram. In one of 43 patients with aortic atresia studied at necropsy by Watson and Rowe (1962), the electrocardiogram had shown pure left ventricular hypertrophy.

The echocardiogram will show a diminutive aortic root and normal left ventricle, but tetralogy of Fallot with pulmonary atresia and large bronchials or truncus arteriosus must be differentiated from aortic atresia and normal left ventricle. Selective aortic and left atrial and left ventricular biplane angiocardiograms are probably needed to define the anatomical features.

Palliation of these patients in infancy will necessitate construction of a pulmonary-aortic shunt, with banding of the pulmonary arteries to prevent intractable congestive heart failure and to prevent pulmonary vascular obstructive disease (Sinha *et al.*, 1968; Cayler *et al.*, 1970; Van Praagh *et al.*, 1971). Atrial decompression may be accomplished in some by balloon septostomy at the time of the diagnostic catheter study. Ventriculoaortic reconstitution might then be accomplished using a valved conduit and repair of the intracardiac defect when the patient is older.

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# Pancarditis affecting the conducting system and all valves in human African trypanosomiasis

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*This paper describes the pathological features of 10 cases of human African trypanosomiasis occurring in Uganda over an 8-year period. Three cases were clinically proved, and in all 10 cases chronic meningo-encephalitis and myocarditis were present. There was chronic pancarditis in 6 cases, and in 3 of these there was a generalized focal valvulitis and in 2 lesions of the conducting system.*

*Previous descriptions of carditis in human African trypanosomiasis are briefly reviewed, and the present findings are compared with some cardiomyopathies as well as American human and experimental trypanosomiasis.*

Although myocarditis in human African trypanosomiasis is not uncommon, detailed histological reports are rare (World Health Organization, 1969; Mulligan and Potts, 1970). Reports from East Africa have described only clinical (Manson-Bahr and Charters, 1963) and necropsy findings (Hawking and Greenfield, 1941; de Raadt and Koten, 1968; Koten and de Raadt, 1969; Hutt and Wilks, 1971). Similarly, Schyns and Janssen (1955), Bertrand *et al.* (1967a, b), and Francis (1972) documented the symptomatology of *T. gambiense* myocarditis including electrocardiographic abnormalities. Lavier and Leroux (1939) and Bertrand *et al.* (1967b) reported on some histological aspects of *T. gambiense* carditis, but in only 2 cases. We report here 10 cases with particular reference to the cardiac lesions.

## Subjects and methods

The 10 cases of human African trypanosomiasis were investigated at the Department of Pathology, Makerere University, Kampala, Uganda, between 1967 and 1974. Two of the cases were of untreated trypanosomiasis, and both had meningoencephalitis and pancarditis. The hearts in these 2 cases were further studied in the Department of Pathology, University of Geneva, Switzerland. The findings are reported below. Then follows a report of a retrospective study of the remaining 8 cases.

## Two-case study

### Case 1

A 36-year-old man of the Dama tribe from Eastern Uganda was transferred from a district hospital to Mulago Hospital 10 days before death with a diagnosis of cerebral malaria. He had had fever for 5 days together with headaches, dizziness, and sweating. Before admission to the district hospital

TABLE *Cardiac morphological features in human African trypanosomiasis from Uganda*

| *Age (y) sex* | *Heart weight (g)* | *Inflammatory reaction of* | | | | |
|---|---|---|---|---|---|---|
| | | *Endo-cardium* | *Myo-* | *Epi-* | *Valves* | *Conducting system* |
| 40 M | 290 | + | + | + | – | – |
| 22 M | 280 | + | + | + | – | – |
| 18 M | 200 | A | + | + | – | – |
| 28 M | 320 | – | + | – | – | – |
| 25 M ● | 250 | + | + | + | – | – |
| 45 M ● | 290 | A | + | A | – | – |
| 20 M | 250 | – | ++ | ++ | – | – |
| 25 M ● | 380 | + | ++ | + | + | – |
| 36 M Case 1 | 240 | x++ | ++ | ++ | ++ | ++ |
| 13 M Case 2 | 180 | x++ | +++ | ++ | ++ | ++ |

A = absent
x = granuloma
● = parasitaemia
– = no blocks or sections or results available
+ = mild
++ = moderate
+++ = severe

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he was unable to walk, sit, or stand or to hold anything in his hands. On admission he was semiconscious, in poor general condition, dehydrated, and febrile at 38°C. His blood pressure was 110/70 mmHg (14·6/9·3 kPa). There was no response to chloroquine and the cerebrospinal fluid showed nothing unusual. As the salmonella H-antigen titre was 1/400 he was treated for typhoid fever but without success. He died on the 11th hospital day. Necropsy was carried out 4 hours after death.

**Necropsy** The patient's weight was 42·6 kg and height 154 cm. No serous fluids were found. The brain (1250 g) showed a diffuse capillary congestion and the cerebrospinal fluid was clear. On section diffuse petechial haemorrhages were seen, mainly in the white matter. The right lung (480 g) and the left (460 g) were mildly congested. There was patchy bronchopneumonia in the upper left lobe. The heart (240 g) was normal in appearance. There were no visible changes on the valves, endocardium, or pericardium. The coronary arteries were patent. The digestive and genitourinary tracts were normal and so were the lymph nodes. The liver (1520 g) and spleen (170 g) were moderately enlarged, but there was no blackish discoloration.

### Case 2

A 13-year-old African of the Lugbara tribe from Northern Uganda, who had been ill for two years, had progressively lost strength and become sleepy. One month before death he was admitted to a mental hospital where blood films were negative for trypanosomes. However, he developed insomnia and became aggressive and confused. A lumbar puncture showed 255 white blood cells, 65 mg/100 ml protein, 45 mg/100 ml sugar, but no trypanosomes. No trypanosomes were seen in the peripheral blood and no trypanocidal treatment was given. Two days before death he was transferred to the neurosurgical unit after a fall. On craniotomy there was no sign of raised intracranial pressure or haematoma.

**Necropsy** The boy weighed 32 kg and was 144 cm tall. He had multiple skin nodules on thighs, arms, left shoulder, and left foot. There were two temporal burr holes but no fracture or signs of infection. The brain was oedematous (1380 g) and the meninges showed capillary congestion. Two fresh haemorrhages were found on the orbital side of the frontal lobes. The lungs (both 450 g) were oedematous and haemorrhagic. The heart (180 g) was flabby with patchy yellowish discoloration of the myocardium on section but there was no abnormality of the four chambers or the valves. Hookworms were present in the gastrointestinal tract. The liver (1370 g) and the spleen (300 g) showed a slight blackish colour on section. The cervical, hilar, mesenteric, and femoral lymph nodes were prominent.

### Histology

The histology of the trypanosomal lesions was almost identical in both cases. Tissue was formalin fixed and paraffin embedded. The following stains were used: haematoxylin and eosin (HE), elastica-Van Gieson, Gram, Ziehl-Neelsen, periodic-acid Schiff (PAS), Giemsa, and Perl's stain.

**Heart** The general picture was that of a pancarditis with severe myocarditis, an endocarditis with occasional granulomata, a moderate but patchy epicarditis, a generalized valvulitis, and lesions of the conducting system.

**The myocardium** (Fig. 1) showed a diffuse interstitial or perivascular cuffing. The inflammatory cells consisted primarily of lymphocytes,

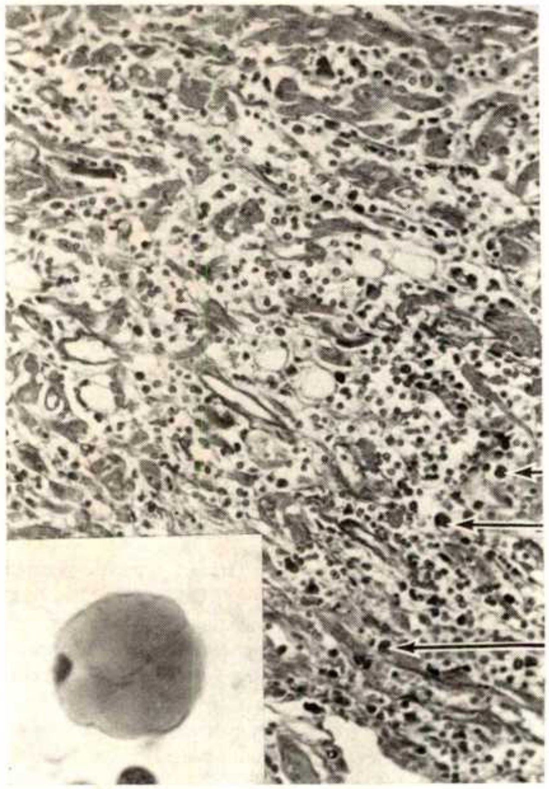

FIG. 1 *Myocardial lesions in human African trypanosomiasis. Severe myocarditis with several morular cells (arrows): one is shown in the inset. (Case 2: PAS × 130.) Inset: Case 1 (HE × 676).*

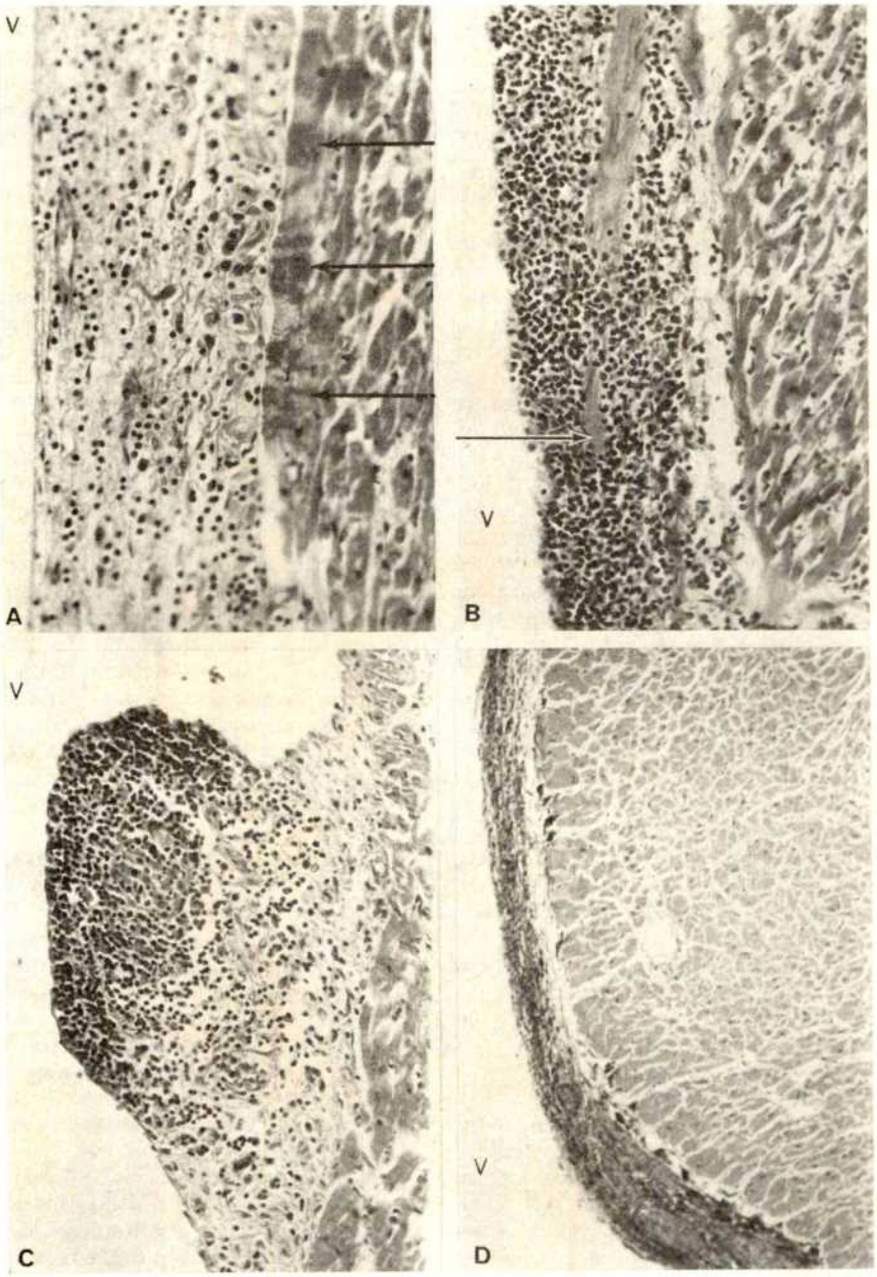

FIG. 2 *Parietal endocarditis and mycocytolysis in human African trypanosomiasis. V= ventricular chamber. (A) Superficial mycocytolysis showing contraction bands (arrows). Oedematous and fibrous thickening of the endocardium with chronic cellular infiltration. (Case 1 : HE×87.) (B) Linear dense infiltration with fragmentation of muscle fibre which leads eventually to granuloma (arrow). (Case 2 : HE×87.) (C) Constituted granuloma with centrally degenerated muscle fibres. (Case 2 : HE×87.) (D) Fibrosing endocarditis. (Case 1 : Elastica van Gieson×33.)*

mastocytes, plasma cells, morular cells, occasional Russell bodies, histiocytes, and Anitschkow cells. There was interstitial oedema. The muscle fibres in some areas showed varying phases of degeneration, sometimes with ballooning of the nuclei or ceroid degeneration of the cytoplasm. There were zones of patchy fibrosis with or without cellular reaction containing pre-existing capillaries with a swollen endothelium in places. Mycocytolysis and contraction bands of the superficial muscle fibres were seen underneath the infiltrated endocardium. In Case 1 the myocarditis was moderate and haemosiderin was found abundantly in histiocytes but not in muscle fibres; there were a few microfilaria of the *Acanthocheilonema perstans* type in the capillaries. In Case 2 there was little haemosiderin pigment but the myocarditis was severe.

**The endocardium** (Fig. 2A, B, C, D) in all four chambers showed patchy thickening and/or fibrosis. The chronic cellular infiltration was linear or focal, with the formation of granulomata. The cellular infiltrate was identical to that in the myocardium. In the centre of the granuloma-like structures there were often fragments of degenerated muscle fibres. There were no giant cells. These lesions were not seen in the myocardium. The histocytes in some of the granulomata contained cytoplasmic bipolar inclusion bodies, the nature of which could not be assessed. Small endocardial thrombi (Fig. 3A) were observed in the subvalvular, retropapillary, and intratrabecular region. In Case 1 there was a larger thrombus overlying a zone of recent superficial myocardial necrosis within the right ventricle. In Case 2, granulomata were less frequent. A focal endocarditis, as previously described, was also noticed in the pars membranosa on the left ventricular side in Case 1 and on the right ventricular side in Case 2 (Fig. 3B, C).

**The epicardium** also showed a similar but moderate and patchy chronic cellular inflammation. There was perineuritis and ballooning of some of the sympathetic ganglion cells with degenerative changes. In Case 2 a thickened epicardium with an occasional villous pattern was noted(Fig. 3D). The coronary arteries as well as the vasa vasorum of the aorta were free of lesions in both cases.

**Valves** In sections from both atrioventricular valves and from the aortic and pulmonary cusps (Fig.4A, B, C, D) there was oedema and various degrees of ballooning of the valve with disorganization of the collagen fibres. Foci of chronic cellular inflammation were observed with occasional morular cells in the valve and at its insertion. The infiltration was linear or patchy and was mainly on the inflow of the atrioventricular and on the outflow side of the semilunar valves. The chordae tendineae were patchily infiltrated (Fig. 3C) and the papillary muscles showed the same lesions as described in the myocardium and endocardium. Iron deposits were found in all valves in Case 1 but they were absent in Case 2. In neither case did the capillaries reach the free portion of the valve.

**The conducting system** (Fig. 5A, B, C, D) showed dense fibrotic tissue in the atrioventricular node associated with a patchy chronic cellular infiltration in Case 1. In both cases the bundle of His was overrun by fibrotic bands and its superior portion was replaced by scar tissue, the cellular infiltration, including morular cells, was moderate at the origin of the right bundle-branch and the left branch was replaced by fibrous tissue. Near the origin of both bundle-branches focal calcium deposits were found.

**Brain** Diffuse, mononuclear meningoencephalitis affected the cerebral hemispheres, the cerebellum and the pontomesencephalic structures. Perivascular cuffing, often containing iron deposits, was most pronounced in the white matter of the cerebral and cerebellar hemispheres as well as in the brain stem. The white matter showed varying degrees of gliosis. The nerve roots of the pontine region showed monocellular inflammation. Morular cells were observed in the white matter and in the meninges.

**Other organs** The lungs were congested and contained foci of bronchopneumonia. The liver showed periportal fibrosis in Case 1. In Case 2 there were multiple schistosome eggs (*S. mansoni*), granuloma formation and slight portal fibrosis, and blackish pigment in the portal tracts and in Kupffer cells. The spleen was congested, with moderate hyperplasia of the germinal centres. Some endophlebitis was present in Case 1 and some blackish pigment in macrophages in Case 2. No glomerular abnormalities were observed in the congested kidneys.

In Case 2 further histological examination showed the following: colonic and mesenteric lymphonodular schistosomiasis, erythrophagocytosis in lymph nodes, diffuse hyperplasia of the bone marrow without deposits of black pigment, chronic skin ulcers of unknown origin and normal adrenals.

### Retrospective study

In the 8-year period (1967–1974) 7445 necropsies were carried out in the pathology department, Makerere. The sex ratio of the cases was, male to female, 7 to 3; 70 per cent were 15 years old or

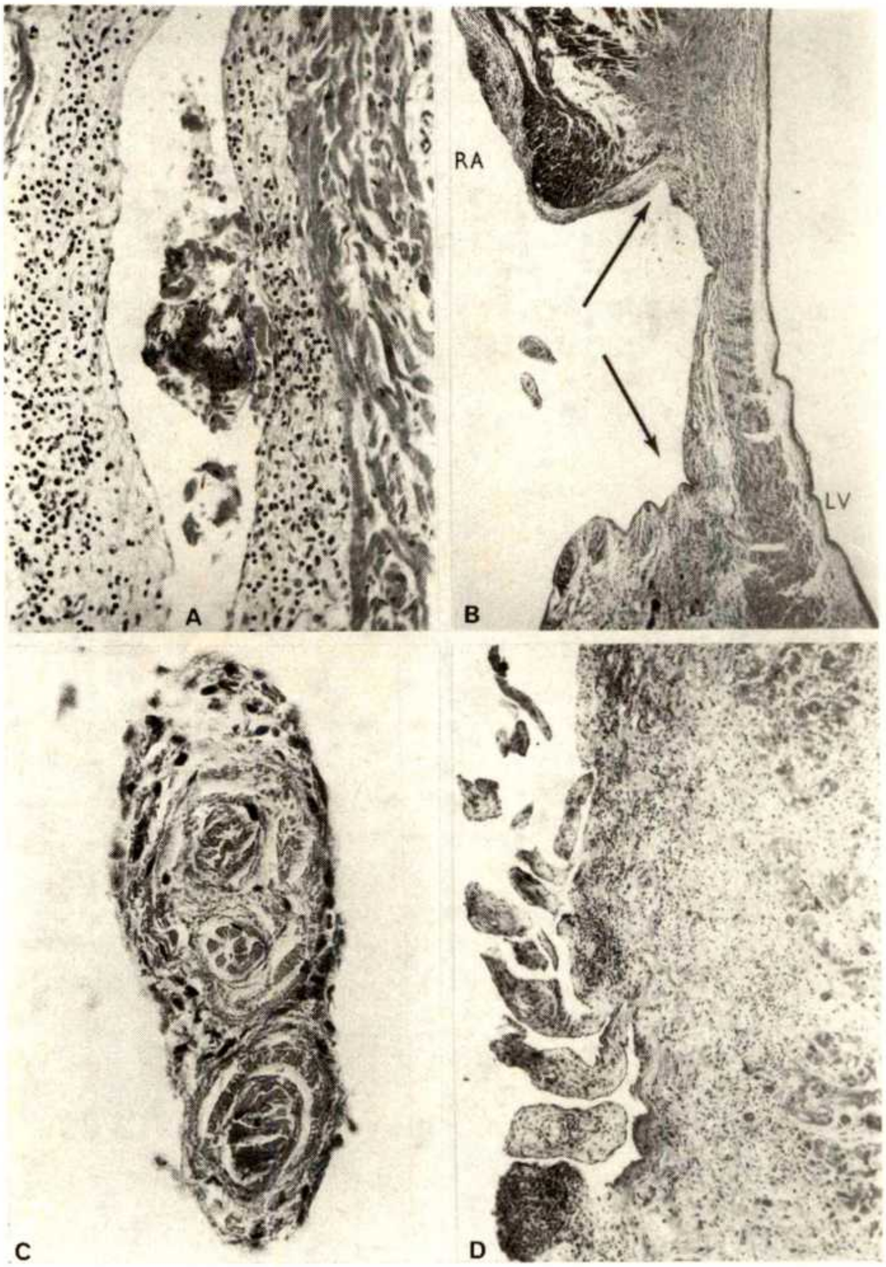

FIG. 3 *Some special cardiac lesions in human African trypanosomiasis. (A) Endocardial thrombosis in intertrabecular space. (Case 1: HE×87.) (B) Pars membranosa showing plurifocal endocarditis (arrows). LV=left ventricle; RA=right atrium. (Case 2: HE×13.) (C) Magnified chorda tendinea of Fig. 3B showing chronic cellular infiltration. (Case 2: HE×270.) (D) Villous pericarditis. (Case 2: HE×33.)*

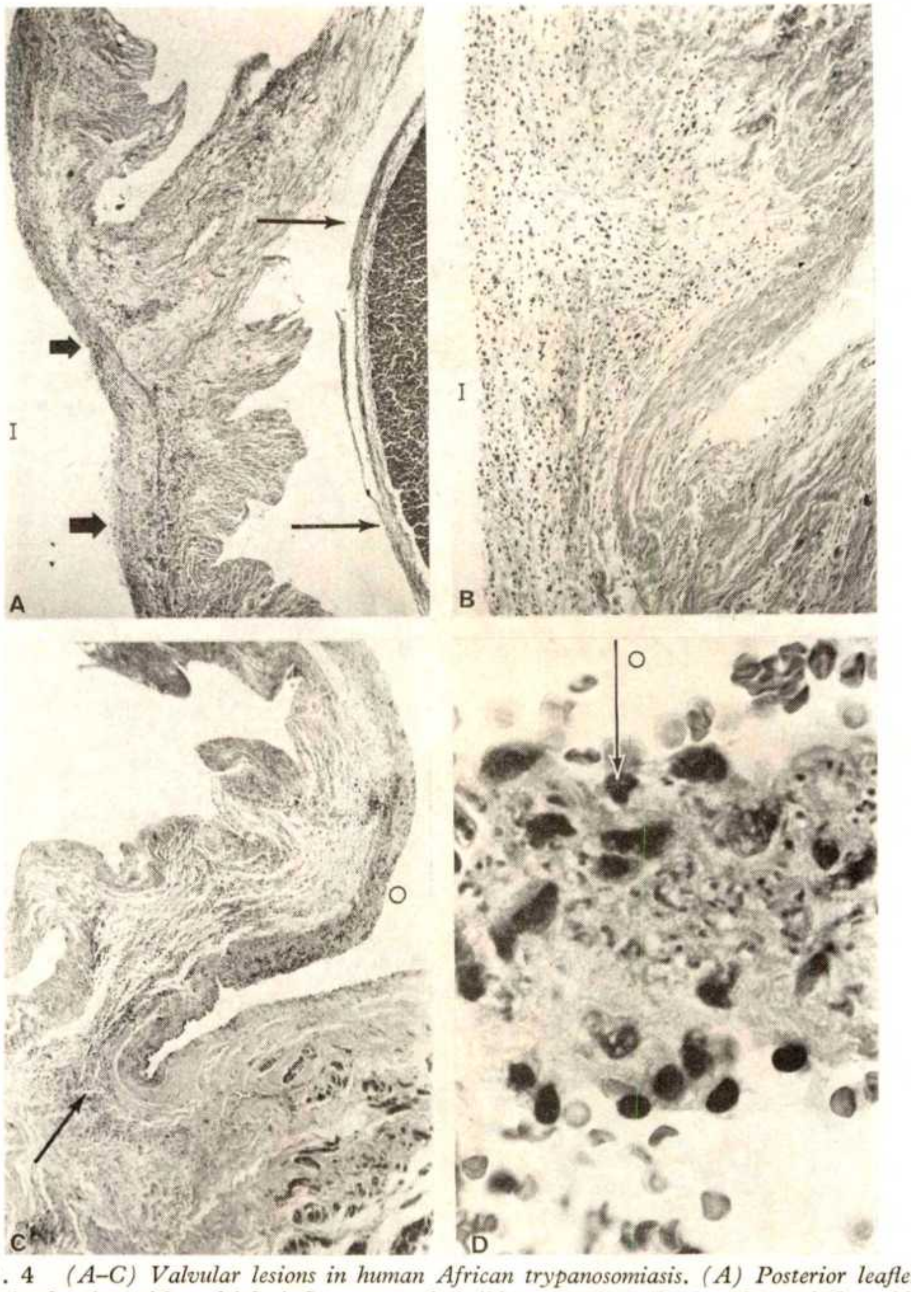

FIG. 4 *(A–C) Valvular lesions in human African trypanosomiasis. (A) Posterior leaflet of mitral valve with multiple inflammatory foci (big arrows) predominantly on inflow side (I). Note retrovalvular parietal endocarditis (small arrows). (Case 2: HE×13.) (B) Posterior leaflet of mitral valve with oedematous and cellular inflammation, the latter mainly localized on inflow side (I). Disorganization of valvular fibres. (Case 2: HE×33.) (C) Pulmonary cusps with focal valvulitis predominantly localized on outflow side (O) and at insertion (arrow). (Case 1: HE×13.) (D) Cardiac valvular lesions in* T.-brucei *infected mouse. O=outflow. Trypanosomal infiltration of pulmonary valve on outflow side. Mononuclear and polynuclear (arrow) infiltration. (HE×670.)*

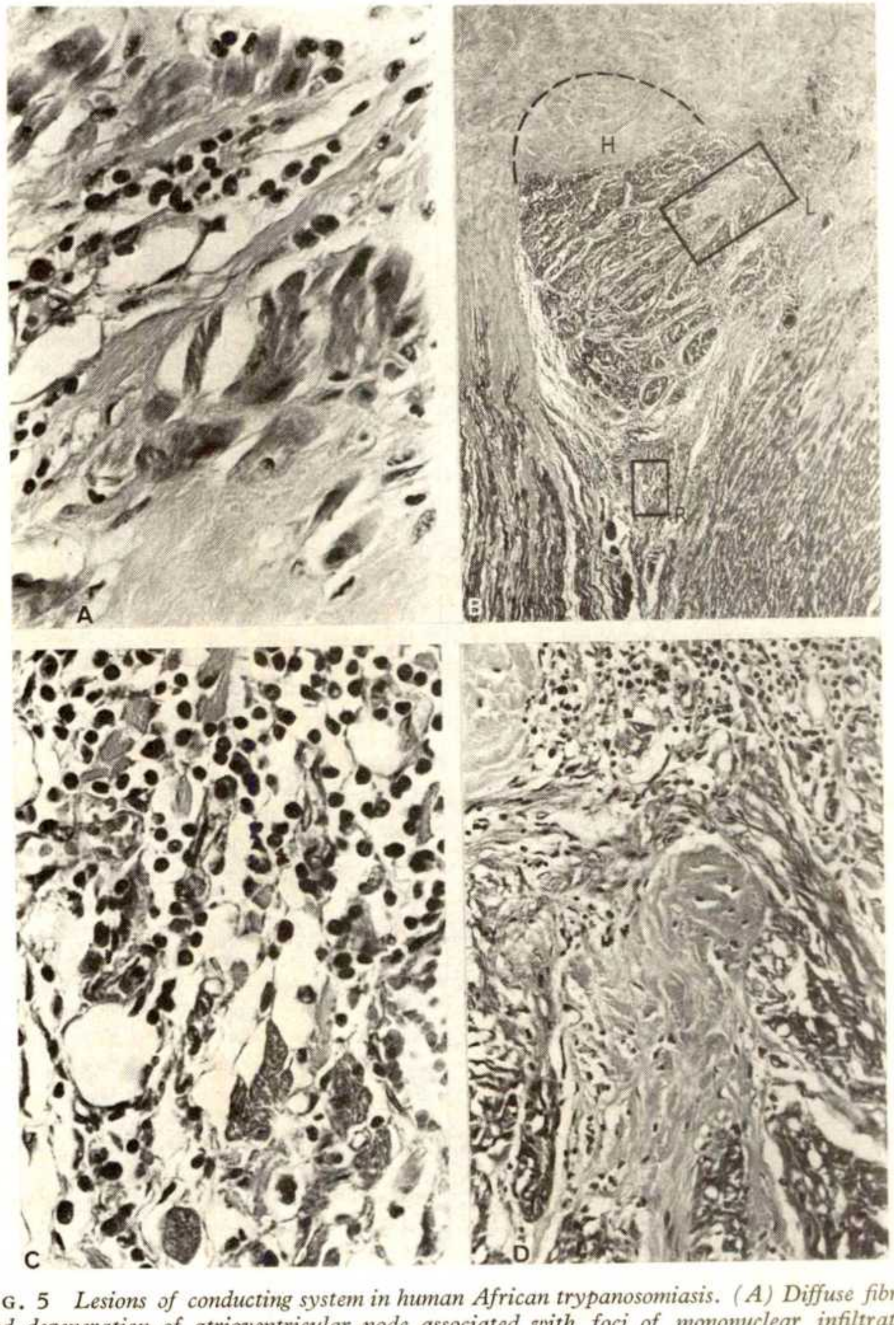

FIG. 5 *Lesions of conducting system in human African trypanosomiasis. (A) Diffuse fibrosis and degeneration of atrioventricular node associated with foci of mononuclear infiltration. (Case 1 : HE×270.) (B) Fibrous amputation of superior portion (broken line) of His bundle (H) and portions of origin of left bundle-branch (L). R=origin of right bundle-branch. Squares indicating origin of bundle-branches as shown in Fig. 5C, 5D. (Case 2 : HE×13.) (C) Right bundle-branch with degeneration of fibres and mononuclear infiltration. (Detail from Fig. 5B : HE×270.) (D) Left bundle-branch showing degeneration of fibres, invasive and dissecting sclerosis, as well as foci of chronic cellular infiltration. (Detail from Fig. 5B : HE×106.)*

more. Twelve cases of human trypanosomiasis were found among those aged over 15 years, so the incidence of trypanosomiasis in adults was 0·16 per cent. Histological findings were unavailable in 4 cases; therefore we report on only 8 of the cases. The findings in the 2 cases already described are excluded here; they are included in the Table.

Trypanosomes were found during life in 3 of the 8 patients and 2 died in spite of trypanocidal treatment. Trypanosomiasis was searched for but no parasites were found in the cerebrospinal fluid in the 5 other patients. The patients were all males aged from 13 to 45 years. All were Black Africans, 4 were of northern tribes (Lugbara), one a Dama from the Eastern Uganda, one a Tanzanian, one a Sudanese, and in 3 the tribe was not recorded. Three of the patients were initially admitted to a mental hospital.

## Necropsy

The fresh brain weight in each of the 8 cases was above 1200 g except in one 18-year-old (1160 g) patient. The following macroscopical changes in the brain were seen: capillary hyperaemia (2 cases), thickening of the meninges (2 cases), and cerebral infarction (2 cases). Histologically there was perivascular cuffing with predominant lymphocytic, plasmocytic, and histiocytic infiltration and morular cells were present.

The weight of the heart in each case was within normal limits except for one, which was moderately hypertrophied (380 g). The valves appeared macroscopically normal in all cases. There was a chronic diffuse and focal myocarditis with predominant lymphocytic, plasmocytic, histiocytic infiltration. In 6 cases these changes were mild and in 2 moderate. Parietal endocarditis was found in 4 cases and morular cells in 1 case. In 1 heart a non-fibrinous valvulitis was seen. A chronic epicarditis was present in 7 cases and absent in 1. An unexplained systemic embolism was seen in the brain in two cases and in the spleen in one case.

In 4 cases an enlarged spleen was associated with hepatic schistosomiasis, and in one case a splenic infarct was associated with parietal endocarditis. There was evidence in the hepatic histology of 'big spleen disease'. Bronchopneumonia was present in 7 cases, severely in 4. No histological evidence of glomerular disease of the kidneys was found.

## Discussion

Human trypanosomiasis is usually diagnosed by finding the parasite at the inoculation site, in lymph nodes, the peripheral blood, or, in the chronic stage, in the cerebrospinal fluid (Hutt, Köberle, and Salfelder, 1973). Otherwise special techniques such as concentration by centrifugation, passage through sephadex columns, serology, immunofluorescence, or inoculation into animals are needed. In sleeping sickness from *T. rhodesiense* the direct evidence of the parasite is usually required before the potentially toxic trypanocidal treatment is given. African trypanosomes have scarcely ever been found in human tissue at necropsy, though the histological changes in the central nervous system are characteristic. In the present series 3 out of 10 cases were proved clinically and the lesions in the remaining 7 were histologically identical. Interestingly, 3 of the patients came from a mental hospital, a presentation stressed by Rwomushana (1973).

The histology of chronic meningoencephalitis in all cases was consistent with that classically described for cerebral human African trypanosomiasis (Mott, 1906; Laveran and Mesnil, 1912; Bertrand, Bablet, and Cicé, 1935; Calwell, 1937; van Bogaert 1958; Hutt and Wilks, 1971). Manson-Bahr and Charters (1963) described *myocarditis* in human African trypanosomiasis, and Schyns and Janssen (1955) had already noted the electrocardiographic abnormalities in the disease in patients from Zaire—a finding confirmed by Bertrand *et al.* (1967a, b) in patients from the Ivory Coast. Histologically, Hawking and Greenfield (1941) noted trypanosomal myocarditis in East Africa, but since then there have been only few reports (de Raadt and Koten, 1968; Koten and de Raadt, 1969; Hutt and Wilks, 1971; Bertrand, 1974). In the present series myocarditis of varying intensity was found in every case in which histology findings were available (Table 1, Fig. 2A) and in general the appearance was similar to that described by others (de Raadt and Koten, 1968; Koten and de Raadt, 1969; Hutt and Wilks, 1971). Morular cells were often found within the cellular infiltration or isolated, a finding previously recorded by Koten and de Raadt (1969). In addition there were zones of mycocytolysis.

The endocardium was thickened and, in more advanced stages, fibrosed; the cellular infiltration was focal or linear with formation of granulomata. Occasional granulomata have been reported in the epicardium (Hawking and Greenfield, 1941) and the myocardium in cases of human African trypanosomiasis (Bertrand *et al.*, 1967b) but not in the endocardium. In this series the granuloma formation consisted of central degenerate muscle fibres surrounded by histiocytes, in some of which there were cytoplasmic inclusion bodies suggestive of trypanosomal origin. In the immediate subendocardial region there often was an extensive myocytolysis similar to that observed in the rest of the myocardium. Acute mycocytolysis presenting with contraction bands is often referred to as Magariño-Torres lesion in human *T. cruzi* carditis (Andrade and Andrade, 1971) and may lead to myocardial granuloma formation (Andrade and Andrade, 1971; Hutt *et al.*, 1973). Intimately associated with the endocardial lesions were microscopical thrombi, and these have also been recorded in human American trypanosomiasis (Köberle, 1968; Andrade and Andrade, 1971; McKinney, 1974), in endomyocardial fibrosis (Shaper, Hutt, and Coles, 1968) and in idiopathic cardiomegaly (Hutt, 1974). Systemic or pulmonary embolism is known to occur in human American trypanosomiasis (Andrade and Andrade, 1971) and in endomyocardial fibrosis (Shaper *et al.*, 1968; Owor, 1973). Possibly the unexplained embolism in this series has its source in the endocardium. Apical aneurysms are known in human African trypanosomiasis (Laranja *et al.*, 1956; Anselmi *et al.*, 1966; Köberle, 1968; World Health Organization, 1969; McKinney, 1974) and they could be produced experimentally (Anselmi *et al.*, 1971). To the best of our knowledge no aneurysms have been associated with human African trypanosomiasis; however, subvalvular aneurysms of unknown origin were described in Black Africans (Edington and Williams, 1968; Poltera and Jones, 1973). We found no aneurysms though the pars membranosa in 2 cases showed focal endocarditis which could have led eventually to aneurysms. Our series confirmed that trypanosomal pericarditis occurs in human African trypanosomiasis. Previous authors are agreed on this, though, curiously, d'Arbela *et al.* (1974) did not mention it in reporting 154 cases.

Although the heart valves appeared macroscopically normal, histology showed a focal or diffuse valvulitis present at the insertion as well as in the leaflets. Hutt and Wilks (1971) stated that the valves were not involved in human African trypanosomiasis and McKinney (1974) reported the same for human American trypanosomiasis. Ferreira and Rossi (1972), however, noted denervation of the valves in human Chagas disease. Valvulitis in human trypanosomiasis has probably been overlooked because of the normal macroscopical appearance and hence the lack of systematic analysis. The chordae tendineae of the atrioventricular valves were equally infiltrated and showed thickening. The papillary muscles showed identical lesions to the myocardium and endocardium, the retropapillary space being occasionally thrombosed. The retrovalvular endocardium of the atrioventricular valves showed an inflammatory infiltration.

Though endomyocardial fibrosis causes pancarditis it remains a cardiomyopathy of unknown origin, though the need for a more intensive search for a toxic or infective agent acting directly on the endocardium and myocardium has been emphasized (Farrer-Brown *et al.*, 1972). Farrer-Brown and Tarbit (1972) showed the avascularity of the affected atrioventricular valves in endomyocardial fibrosis and they described for the first time the involvement of a pulmonary valve in this disease. Previously the semilunar valves were thought never to be involved (Edington and Gilles, 1969; McKinney, 1974). The association of endomyocardial fibrosis with subvalvular aneurysms has been recorded (Robertson and Jackson, 1960; Poltera and Jones, 1973). Armengaud and Diop (1960) reported cases of cardiomyopathy with heart failure from Senegal in which trypanosomes were identified in the blood and who responded to trypanocidal treatment. Similarly, Blackett and Ngu (1976) observed in the Cameroons congestive cardiomyopathies with an exceedingly high serological titre for trypanosomiasis.

Modifications in cardiac conduction and rhythm are often found in chronic and, to a lesser extent, acute human American trypanosomal carditis (Rosenbaum, 1964; Andrade and Andrade, 1971). Clinical reports on electrocardiographic abnormalities in African Gambian trypanosomiasis are uncommon (Bertrand *et al.*, 1967a, b; Francis, 1972) and apparently almost non-existent in the Rhodesiense type. Lavier and Leroux (1939) described cardiac perineural cellular infiltration in one Congolese case and Bertrand *et al.* (1967b) showed a right bundle-branch block in one case from the Ivory Coast. In the present series multiple focal lesions were found in the conducting system in two hearts, either in the atrioventricular node, the bundle of His, or within the bundle-branches, and they presented as chronic cellular infiltrates including occasional morular cells or as fibrosing changes in or around the fibres of the conducting system. In both hearts both bundle-branches were involved. It is possible that an inflammatory involvement of the sinus node, similar to the lesions of the conducting system in this series, might contribute in human African trypanosomiasis to a sick sinus syndrome. Such a syndrome of unknown origin has recently been reported in young patients from Uganda (Ikeme, D'Arbela, and Somers, 1975).

Although African trypanosomes have only been once seen in a human heart (Hawking and Greenfield, 1941), there is old experimental evidence of their presence in trypanosomal myocarditis (Wolbach and Binger, 1912; Peruzzi, 1928; Regendanz and Hoeppli, 1929). In simian African trypanosomiasis Peruzzi (1928) showed leishmanoid forms in the myocardium, and Hoeppli and Regendanz

(1930) differentiated the intravascular presence of flagellated trypanosomes in the heart and the extravascular presence of leishmanoid forms between the muscle fibres consisting of a trypanosome nucleus and a blepharoblast with scanty protoplasm. Similarly, Omerod and Venkatesan (1971a, b) confirmed the presence of amastigotes in the heart (1971b). However, no cystic forms were noticed, and this contrasts with the *T. cruzi* infection (World Health Organization, 1969). A review of the pathology of experimental trypanosomiasis (Losos and Ikede, 1972) and Murray *et al.* (1974a) did not mention endocardial valvulitis. Rats infected with *T. brucei* showed electrocardiographic abnormalities (Murray *et al.*, 1974a), but the authors did not mention the conducting system nor did they state the arrhythmic change in the electrocardiogram. In mice infected with *T. brucei* we observed in the acute phase a severe valvulitis (Fig. 4D) and the usual pancarditis.[1] Trypanosomes in the valve were mainly on the flow side and there was subacute cellular infiltration, including red blood cells. Strikingly, the trypanosomes were found at the same site as the inflammatory foci in the present series. Lambert and Houba (1974), in experimentally infected mice, noted a disseminated vasculitis, and their immunological results suggested that immune complexes form in the blood as well as in the extravascular spaces, best seen in the target organs such as brain, heart, and kidney. But it was also shown experimentally in rats and in mice that the immune system was heavily depleted (Urquhart *et al.*, 1973; Murray *et al.*, 1974b, II).

To summarize, we conclude that human African trypanosomiasis is a generalized disease affecting the brain and the pancardium. It also affects the heart valves, the conducting system, and the sympathetic cardiac ganglia. The immune defence system is also affected, but the type of reaction seems to be time-dependent (Urquhart *et al.*, 1973; Murray *et al.*, 1974a). More research is needed to evaluate the possible aetiological role of human African trypanosomasis in the development of cardiomyopathies such as endomyocardial fibrosis and idiopathic cardiomegaly, particularly since trypanosomiasis has now a tricontinental (African, American, and Asian) distribution (Shrivastava and Shrivastava, 1974; Weinmann, 1974; Dissanaike, Ong, and Kan, 1974) and can occur as an imported disease (Spencer *et al.*, 1975).

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# Pathology of hearts after aortocoronary saphenous vein bypass grafting for coronary artery disease, studied by post-mortem coronary angiography

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*A detailed pathological study was made in 10 patients dying up to 13 months after aortocoronary saphenous vein bypass grafting for coronary atherosclerosis. The coronary arteries and vein grafts were investigated by injection with a radio-opaque mass, radiography, dissection, and histology.*

*The report is to some extent historical since the patients died during a period when the operation was first being introduced into two cardiothoracic hospitals. About 80 operations were performed during the time the 10 deaths occurred, a mortality of 12·5 per cent (including cases followed up to 13 months after operation). Seven of the patients were operated on for intractable angina and 3 with a view to aneurysmectomy. All the patients selected for operation were severely disabled despite medical treatment.*

*The main cause of death was extremely severe coronary artery disease and its effects on the left ventricle; in one case, over two-thirds of the left ventricle had been destroyed by infarction before operation. Other causes or contributing causes of death were pulmonary embolism, myocardial infarction complicating angiography (ostial stenosis), and cerebral damage.*

*Ten of the 14 vein grafts (71%) were patent at necropsy. A free flow of injection medium usually occurred between patent grafts and coronary arteries. Thrombosis of a graft was thought to have contributed to death in 3 patients, but not in a fourth who died of pulmonary embolism. Since thrombosis of grafts was usually secondary to poor run-off of blood into severely atheromatous coronary arteries, this was also an indirect effect of the advanced coronary arterial disease. In one case, thrombosis followed severe chronic intimal thickening of a graft in place for 13 months.*

*The study of these deaths emphasizes that in some patients the pathological changes in the coronary arteries and left ventricle are too severe for them to benefit from surgery. Vein grafts cannot be expected to distribute blood effectively through grossly narrowed coronary arteries. In addition, when a large part of the left ventricle is infarcted or scarred, it is almost certain that improving the blood supply by grafting will not result in significant regeneration of cardiac muscle.*

*Since the time when this study was made, there have been few deaths among the many vein graft operations subsequently carried out in the hospitals involved. The two most important factors thought responsible for the improvement are the selection of cases more suitable for surgery by continued improvement of diagnostic techniques, and also the employment of more radical surgical procedures in the form of coronary endarterectomy and the insertion of more grafts per patient.*

A major advance in the treatment of ischaemic heart disease has been the introduction of aortocoronary bypass surgery, using autologous saphenous vein grafts (Favaloro, 1968, 1970, 1972; Favaloro *et al.*, 1970; Johnson *et al.*, 1969, 1970b; Johnson, Auer, and Tector, 1970a; Grondin *et al.*, 1971a, b, c, d, e; Alderman *et al.*, 1973). The operation is performed mainly for very severe angina pectoris resistant to medical treatment. The hospital mortality is low, and patients are commonly freed of their angina and able to return to work (Gott, 1974; Anderson *et al.*, 1972; Cooley *et al.*, 1973). Sometimes an internal mammary

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artery is used instead of a vein graft, mainly for the anterior descending artery (Green, 1972). It is generally agreed that the operation should be performed only in specialized centres, where clinical facilities include investigation by coronary angiography by the method of Sones and Shirey (1962) and where the operative mortality is usually less than 5 per cent (Balcon *et al.*, 1974).

The necropsies described here were performed during a period when the operation, which originated in the United States, was being introduced into two cardiothoracic hospitals in London. In order to determine as precisely as possible why these particular patients had not benefited from surgery, a detailed study of the hearts was made, including post-mortem coronary and vein graft angiography followed by radiography, dissection, and histological examination.

## Subjects and methods

Ten patients died between 1 January 1971 and 31 December 1972. Full necropsies were performed on 8 of the patients but the heart only was examined in Cases 2 and 3. At the time of necropsy, special care was taken while opening the thorax since sometimes an anterior vein graft was found to be adherent to the back of the sternum. The heart was removed intact and preserved deep-frozen until 12 hours before the injection time, when it was thawed slowly in a refrigerator at 4°C.

For the vascular injections, small cannulae were tied into the origins of the coronary arteries and/or into the aortic ends of the saphenous vein grafts. The injection mass was composed of 'Micropaque' (Damancy and Company, Ltd.) 330 ml, gelatin powder 33 g, water 130 ml, and a few crystals of thymol, and was prepared well in advance. The heart and also a bottle containing the injection mass were warmed in hot tap water at 50 to 55°C, and the mass was then injected at a pressure of 120 mmHg (16·0 kPa) (supplied by a cylinder of compressed air) for 20 minutes. The heart was then cooled in iced water, with the injection pressure maintained, and was fixed in formol saline. During the injection procedure, intercommunications between vein grafts and coronary arteries were tested by perfusing certain vessels separately and observing reflux in others. The composition of the injection mass was such that it filled only vessels down to 50$\mu$ internal diameter, which was ideal for the present purpose; injecting smaller vessels would have obscured the larger vessels by a haze in $x$-rays. Several transverse slices about 0·5 cm thick were cut from the lower halves of the ventricles, starting at the apex, and then the base of the heart was opened out for radiography by the 'unrolling' dissection technique of Schlesinger (1938). The tricuspid and mitral valves were removed intact for a separate study.

Radiographs of all slices and of the unrolled bases were taken with an A.E.I. Raymax 50 Superficial Therapy Unit in a lead-screened cabinet. Exposure times were between 30 and 45 minutes at 30 kV and 3 mA, using Kodaline standard film and Kodak D11 or D76 developer.

The condition of the grafts and coronary arteries was also determined by dissection, using the radiographs as a guide and making notes on paper tracings of them. Blocks of tissue were embedded in paraffin wax and sections were stained with haematoxylin and eosin, and with Verhoeff's elastic and van Gieson's stains. Recent infarcts were stained by the HBFP method[1] (Lie *et al.*, 1971; Nayar and Olsen, 1974).

## Results

There were 10 cases, 9 men and 1 woman, and their ages ranged from 41 to 63 (mean 54·9) years.

### Case 1

A man of 57 years suffered from stable angina pectoris for 5 years; during the last 6 months of his life he became almost totally incapacitated by angina which was resistant to medical treatment. Surgery was offered as the only hope of relief, and coronary cineangiography was performed as an essential step before vein grafting. During this procedure he developed ventricular fibrillation, and at an emergency operation two reversed saphenous vein grafts were inserted from the aorta into the anterior and posterior descending coronary arteries. However, part of the left ventricle was found to be newly infarcted, and he died shortly after operation from irreversible ventricular fibrillation.

At necropsy, the heart weighed 425 g. The ostia of both left and right coronary arteries were found to be severely stenosed by atherosclerosis and cannulae could be inserted only with difficulty. There was no reverse flow of medium in the vein grafts when the coronary arteries were perfused (an occasional occurrence observed by others). However, the grafts were patent and were cannulated at the aortic end and perfused separately. Radiographs showed that the left coronary artery was dominant; the right coronary artery was short and did not reach to the posterior interventricular sulcus. The

[1] Haematoxylin, basic fuchsin, picric acid (Lie's stain).

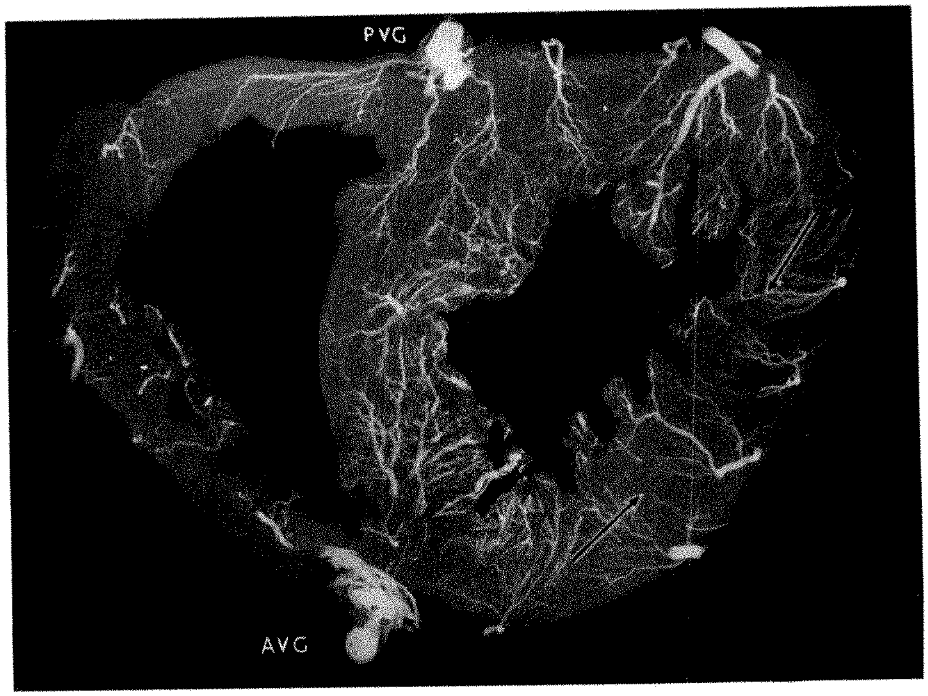

FIG. 1 *Case 1. Radiograph of slice through ventricles viewed from above. Posterior vein graft (PVG) communicates with branches of posterior descending artery. Anterior graft (AVG) has leaked during post-mortem injection. There are prominent anastomoses in interventricular septum, with large subendocardial vessels. Anterolateral part of left ventricle (lower right quadrant) shows deficient vascular filling (between arrows), corresponding with infarcted area noted at operation and confirmed histologically.*

circumflex branch of the left coronary artery was moderately atherosclerotic, with only a little narrowing, and supplied the posterior descending artery which was patent also. The anterior descending branch of the left coronary artery was very severely narrowed by atherosclerosis near its origin, and the minute lumen was discovered only by microscopy. No thrombi were found in any coronary arteries. The vein grafts were patent throughout. The infarct noted at operation was visible in the post-mortem angiogram as a zone of deficient vascular filling in the anterolateral wall of the left ventricle (Fig. 1); this corresponded with the infarct observed at operation. No changes could be found in the haematoxylin and eosin sections because the infarct was so recent; however, infarction was shown successfully by HBFP stain. The injection and fixation technique precluded the use of enzyme methods. There was a fibrous scar in the interventricular septum.

Transverse histological sections of the coronary arteries immediately proximal and distal to the graft insertions showed the following internal diameters: anterior descending artery, proximal to graft insertion 1·08 mm, distal 0·91 mm; posterior descending artery, proximal to graft insertion irregular and less than 0·9 mm, distal 0·57 mm. Some allowance should be made, in interpreting these figures, for tissue shrinkage in histological processing. Sections of the vein grafts showed no abnormalities.

The lungs were oedematous (left 700 g, right 675 g), and in the stomach there was a peptic ulcer.

**Comment** The patient's angina was almost totally incapacitating and was unresponsive to medical treatment. Pathologically there was very severe atherosclerotic narrowing of the ostia of both left and right coronary arteries, and of the anterior descending artery. Myocardial infarction occurred during coronary angiography, probably because of the ostial disease, and the patient died in spite of emergency vein grafting. Post-mortem coronary angiography showed patent vein grafts and poor vascularity of the anterior left ventricular wall, and staining for recently infarcted muscle was positive.

### Case 2

A man of 55 years suffered from angina for 5 years and an attack of myocardial infarction occurred 3 years before death. During the last year of his life he had severe angina and dyspnoea on only slight exertion. Examination showed signs of advanced aortic valve disease, and coronary angiography showed a block in the anterior descending artery. At operation, the aortic valve was replaced and an aortocoronary vein graft was inserted into the anterior descending artery. The left coronary ostium was large and easily perfused, but the right coronary ostium was too narrow for cannulation at operation. The aortic valve cusps showed 'floppy valve' disease. There was fibrosis of the left ventricular myocardium. The heart arrested several times during the postoperative period and he died 8 days later.

The heart only was examined at necropsy and weighed 505 g. A pink polypoid recent ante-mortem thrombus lay in the narrowed ostium of the right coronary artery. A cannula was inserted with ease into the left coronary artery but with difficulty into the right. The whole length of the vein graft to the anterior descending artery contained thrombus. In the post-mortem angiograms, the right coronary artery was filled irregularly with injection mass and was blocked completely near its junction with the posterior descending artery (Fig. 2); dissection showed atherosclerotic calcification with severe narrowing at this point, and there was thrombus partly filling the lumen of much of the main vessel proximally and blocking it at the site described above; the posterior descending artery was very narrow. The left main coronary artery was also atherosclerotic and the anterior descending branch was narrowed to 1 mm at a point about 3 cm above

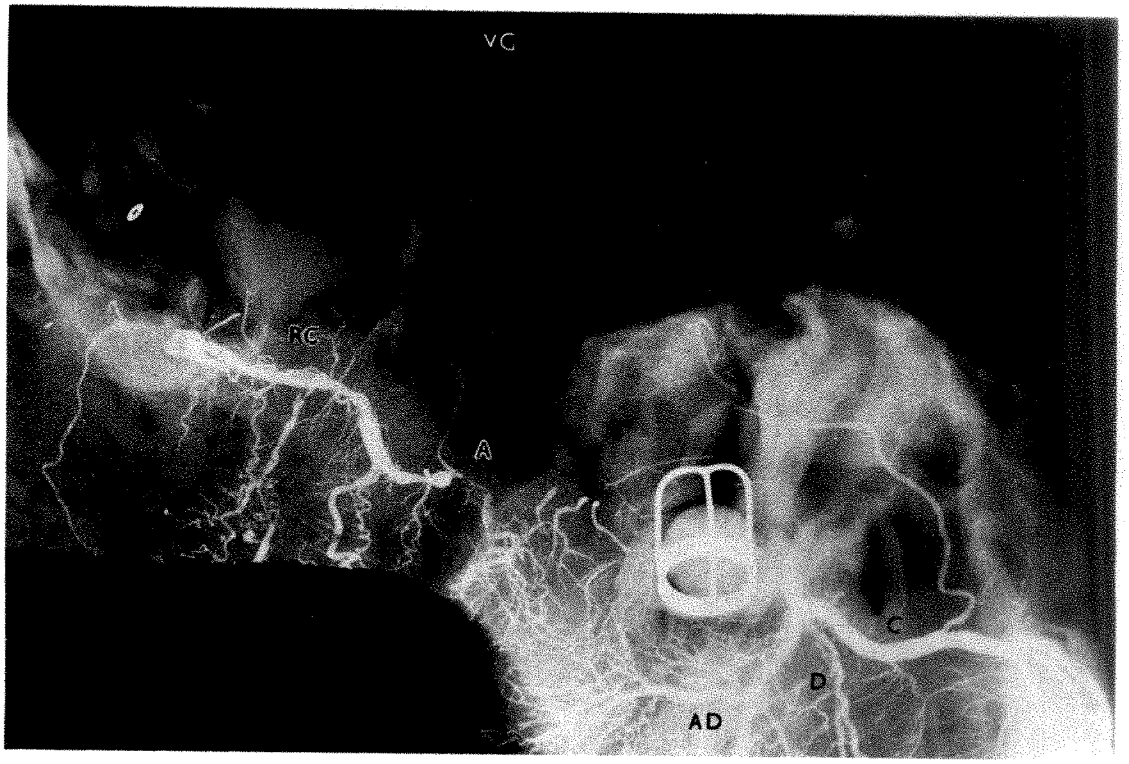

FIG. 2 *Case 2. Radiograph of 'unrolled' heart with right ventricle to left. Prosthesis replaces aortic valve. Right coronary artery (RC) is irregularly narrowed by atherosclerosis and partial thrombosis, and is blocked (A) where it joins posterior descending artery. Occluded vein graft, with distal end cut, has been moved upwards (VG). Narrowing of anterior descending artery (AD), and diagonal branch (D). Circumflex artery (C) is only mildly atheromatous. See also Fig. 3.*

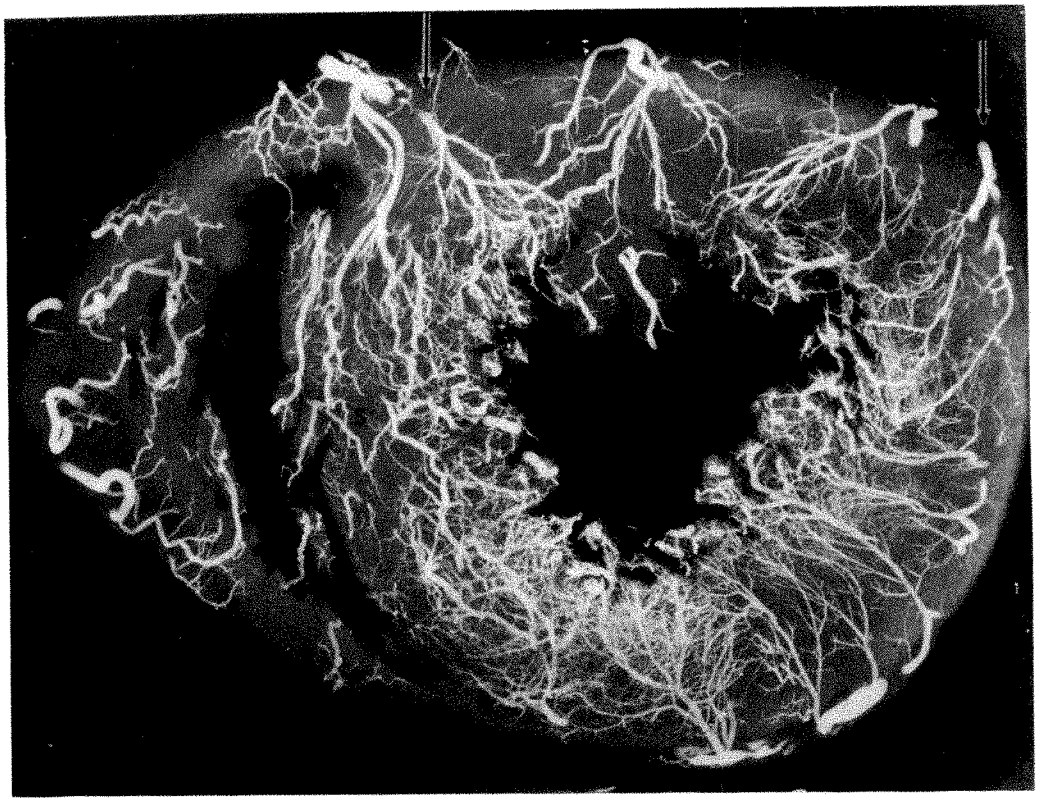

FIG. 3 *Case 2. Radiograph of slice through ventricles showing deficient vascular filling in infarcted posterior wall of left ventricle (between arrows) in territory of recently thrombosed right coronary artery. Note hypertrophic thickening of left ventricle and prominent anastomoses in interventricular septum (S).*

the vein graft. There was a band across the lumen of the left circumflex branch near its distal end, indicating previous thrombosis, but no acute lesion was found and the vessel elsewhere showed only mild atherosclerosis. A diagonal artery was severely narrowed.

The left ventricle was hypertrophied and showed severe ischaemic fibrosis of its posterolateral part; there was also extensive fibrosis of the septum. In radiographs, most of the slices showed poor filling of fine vessels in the posterior wall of the left ventricle (Fig. 3), and in the lateral wall also in some slices. These changes were attributed to thrombosis of the right coronary artery.

Histologically, the anterior descending artery was atheromatous near the graft and measured 1·37 mm internal diameter proximally and 1·07 mm distally. The thrombus at the mouth of the right coronary artery showed platelet laminae, and was not organized; a similar thrombus was seen in sections of the same vessel further along. The thrombus in the vein graft to the anterior descending artery was cup-shaped and laminated near the aortic end, as if formed in a moving blood stream, while further down it had the appearance of a simpler static clot. Sections of the left ventricle showed fibrosis and early infarction, and the HBFP stain was positive.

**Comment** This patient with severe angina died 8 days after aortic valve replacement and insertion of vein graft into the anterior descending artery. Death was the result of thrombosis of the graft and of the right coronary artery. The function of the left ventricle was adversely affected by three factors, viz. recent infarction, scarring from previous infarctions, and possibly altered dynamics caused by aortic valve replacement. The thrombosis of the right coronary artery resulted from severe atherosclerosis at several sites but especially at the ostium which not only slowed blood flow, but also prevented this vessel from being perfused during the operation. The cause of thrombosis in the vein graft was not certain, though the run-off vessels were atheromatous and rather narrow.

### Case 3

A man of 59 years had an attack of myocardial infarction 19 months before death and subsequently developed a left ventricular aneurysm, for which surgery was required. A coronary angiogram showed severe stenosis of the origin of the right coronary artery. At operation the aneurysm was resected and a vein graft was inserted into the right coronary artery. Early postoperative blood loss was controlled with a transfusion of fresh blood. Infection of the lungs and of a wound haematoma complicated convalescence and he died suddenly 3 weeks after operation, despite defibrillation.

Only the heart was available for study; it weighed 605 g and was covered by brown adhesions which held the vein graft lightly to the surface of the heart. The vein graft was patent. The suture line in the left ventricle was satisfactory. The orifices of coronary arteries were narrow; when the mass was injected into them using fine cannulae, it returned up the vein graft, which was then ligated at the aortic end to conserve injection pressure.

Radiography and dissection of the heart showed that beyond the ostial stenosis, the right coronary artery was widely patent, and there was a wide opening into the graft; there was some narrowing of the posterior descending artery at one point. The left coronary artery was also narrowed at its origin, and there was very severe atherosclerosis of the anterior descending, circumflex, and diagonal branches. There was deficient vascularization of part of the left ventricle in the radiograph of the 'unrolled' specimen (Fig. 4). On dissection, the left ventricle showed extensive ischaemic fibrosis of the lateral and posterior walls, involving much of the endocardium and also some of the papillary muscles (aneurysm resected surgically). Mural thrombus was present. About one-third of the muscle of the

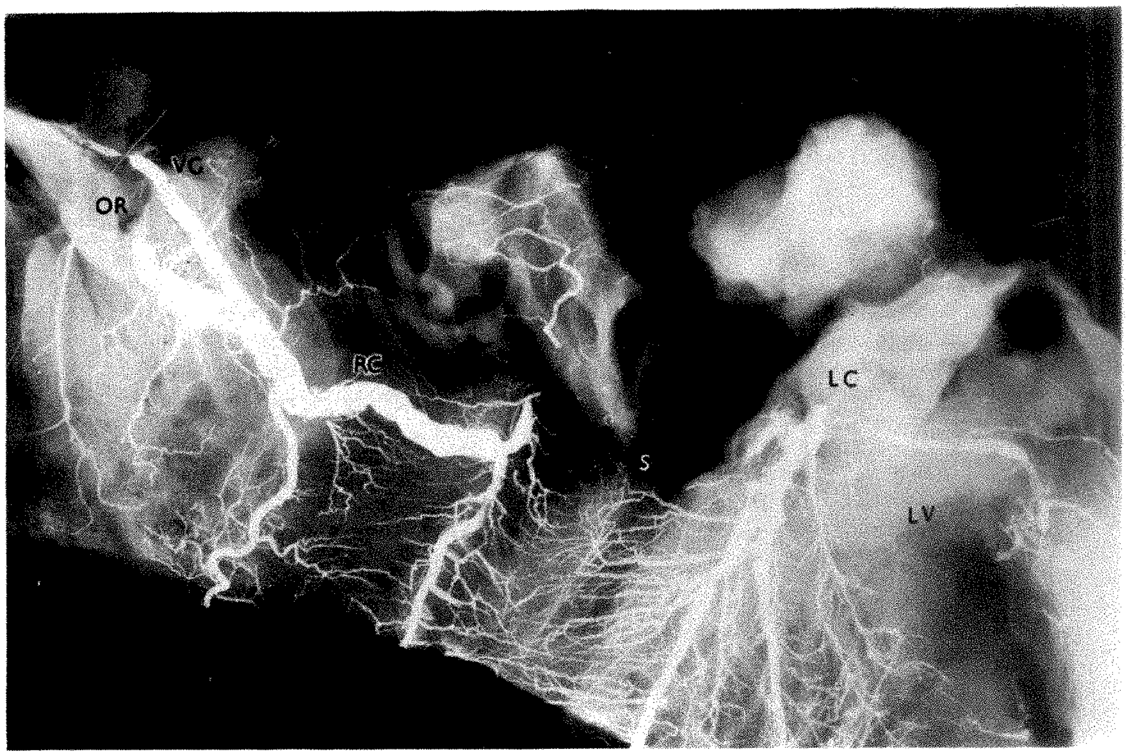

FIG. 4 *Case 3. Radiograph of 'unrolled' heart with right ventricle to left. Vein graft (VG) is patent and supplies broad right coronary artery (RC) which was narrowed near its origin (OR). Conspicuous septal anastomoses (S). Left coronary artery (LC) and branches are severely narrowed and much of left ventricle shows deficient vascularization (LV).*

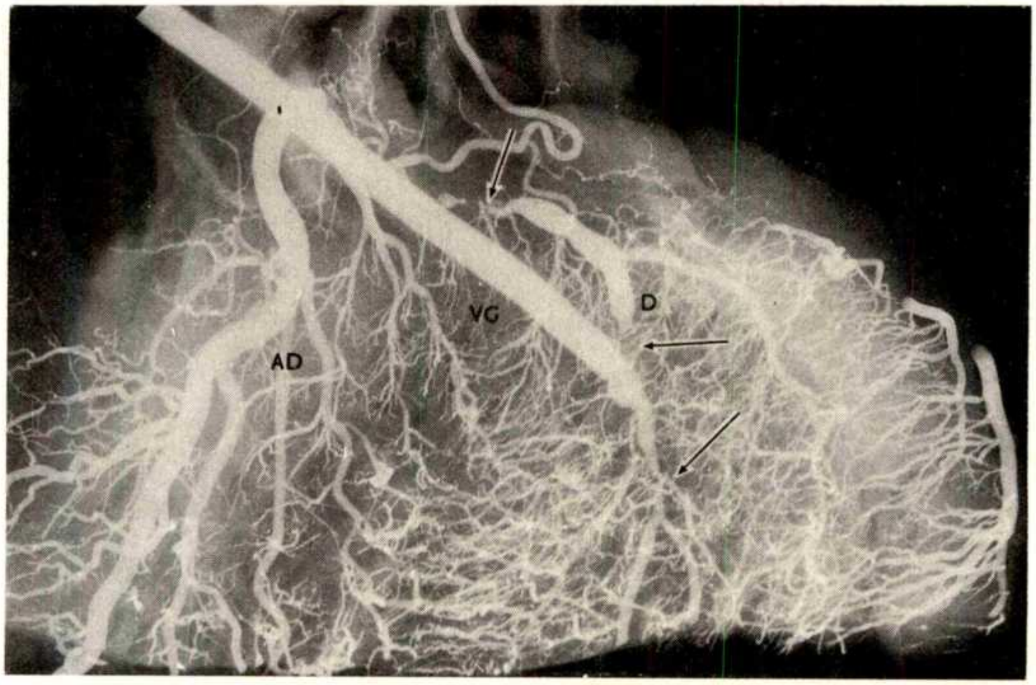

FIG. 5 *Case 4. Radiograph of left ventricle showing patent vein graft (VG) entering diagonal artery (D). Severe narrowing of lateral branch of circumflex artery by atherosclerosis at a point 3 cm and also immediately above and below graft (arrows). Anterior descending artery (AD) is less atheromatous.*

left ventricle appeared fibrosed.

Histologically, the vein graft appeared patent and was lined by a layer of viable endothelial cells. The media was viable and slightly thickened. The adventitia was joined to epicardial fat by organizing fibrin in which there were small foreign bodies, some of them doubly refractile, which had caused granulomata to form. There were also small collections of neutrophils, and around vessels some way from the adventitia there were collections of lymphocytes and plasma cells. The fibrosis of the left ventricle was old and ischaemic in appearance, and there was no histological evidence of recent infarction. The HBFP stain was negative for infarction. However, the post-mortem angiogram showed poor perfusion of a wide area of the left ventricle (Fig. 4), suggesting greater ischaemic effects terminally than was evident from the histological appearance of the muscle. This poor perfusion may explain his sudden irreversible cardiac arrest.

**Comment** As far as can be made out from pathological examination of the heart alone, the cause of death three weeks after operation was failure of the left ventricle caused by extensive ischaemic fibrosis involving more than one-third of the muscle (aneurysm excised). This was caused by multiple atherosclerotic narrowings of both coronary arteries. A single vein graft to the right coronary artery (for ostial stenosis) was patent. There was no acute infarction of the left ventricle histologically.

### Case 4

A man of 59 years suffered from angina of effort for 10 years, and this had become increasingly severe during the previous year. Coronary angiography showed stenoses of the right coronary artery, and poor filling of the left circumflex artery. Vein grafts were inserted into the right coronary artery and lateral branch of the left circumflex coronary artery, but on the day after operation, he became unconscious, and remained so until death 10 days later.

Necropsy showed cerebral oedema and haemorrhages, pulmonary oedema, chronic congestion of the liver, and prostatic enlargement. The heart weighed 380 g and was covered by brown adhesions. Both grafts were patent. When medium was injected into the vein graft to the right coronary artery it returned up that artery, which was then ligated to conserve pressure. Similarly, injection of the vein graft to the lateral branch of the left circumflex coronary artery was followed by reflux from the left main coronary artery, which also was ligated.

Dissection and radiography showed extensive atherosclerosis of the coronary arteries receiving the grafts which would probably have limited their usefulness had the patient lived longer. The internal diameter of the right coronary artery was narrowed to 2 mm proximal to the vein graft and to the same extent at a point about 1 cm distal to the graft. The left main coronary artery was widely patent, but the lumen of the lateral circumflex artery was reduced to 1 mm in diameter immediately proximal to the graft entrance, to about 0·5 mm at a point 3 cm proximal, and to a similar extent 1·5 cm distal to it (Fig. 5). The anterior and posterior descending arteries were less atheromatous. The fine left ventricular vessels were well filled with medium. The lateral wall of the left ventricle was scarred from apex to base, associated with the severe atherosclerosis of the lateral circumflex artery. Histologically, the grafts were viable and the endothelium was intact; the intima showed a trace of thickening.

**Comment** The patient suffered from severe angina for 10 years. He died 10 days after operation from cerebral changes. Both vein grafts were patent at necropsy. Severe coronary disease was present both proximal and distal to the anastomoses, and there was ischaemic fibrosis of part of the left ventricle.

### Case 5

A woman of 65 years suffered from angina for 8 years, becoming worse latterly. Aortic valvular stenosis was present. Coronary angiography showed several major stenoses of the right coronary artery and some less severe stenoses of both branches of the left coronary artery. At operation, a vein graft was inserted into the right coronary artery and an aortic valvotomy was performed. The vein graft was turned inside out to remove valves so that the smaller end could be inserted into the coronary artery. Subsequently there was only slight improvement in the

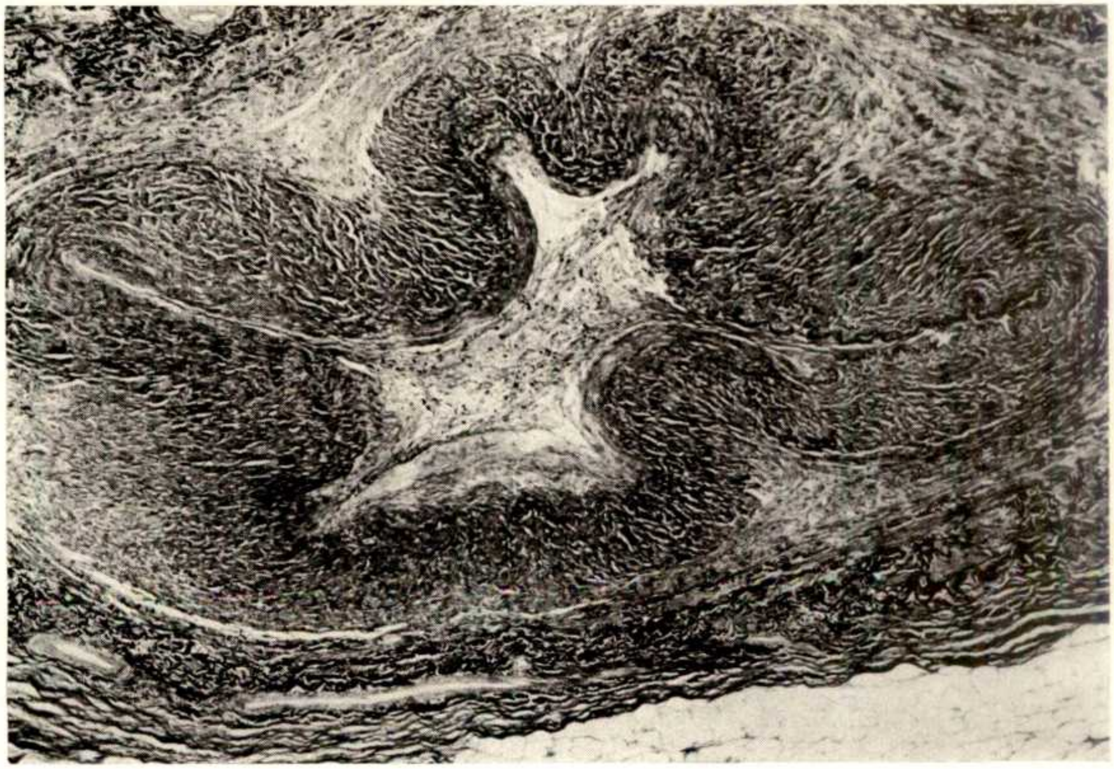

FIG. 6 *Case 5. Vein graft showing old occlusion of lumen by delicate connective tissue containing siderotic histocytes seen as small dots. Corrugations of media result from inward collapse of graft. (Elastic-van Gieson. ×55.)*

angina, and the patient died in heart failure 6 months later.

At necropsy, the vein graft to the right coronary artery was found to be collapsed and was occluded completely by pale tissue. (No medium was injected into the coronary arteries because of an accidental cut in the wall of the right ventricle.) The ostium and main stem of the right coronary artery showed severe narrowing by atherosclerosis. The left main coronary artery was widely patent, but the first 5 cm of the anterior descending artery was calcified and extremely narrow, and the left circumflex artery was very narrow at a point 3 cm from its origin; the severity of the disease seemed to have increased since the cineangiogram 6 months previously. The left ventricle was 15 mm thick, and showed a small focus of fibrosis in the anterior wall, involving papillary muscles. There was calcific aortic valve disease (treated by valvotomy). Pulmonary oedema and 'nutmeg' liver were the main changes in other organs.

Histologically, old organized thrombus filled the lumen of the graft (Fig. 6), and there were some siderotic histiocytes in the small amount of dense organizing connective tissue present. The intima showed fibroelastic thickening, and was corrugated and collapsed inwards. Suture material and other foreign matter were present in the adventitia, causing the formation of reactive granulomata. A section of left ventricle showed recent infarction as well as old fibrosis. The HBFP stain was positive for infarction. No recent thrombi were found in sections of coronary arteries.

**Comment** This woman died from the effects of very severe atherosclerotic narrowing of all 3 principal coronary arteries, and aortic valve disease. A vein graft, inserted into the right coronary artery at the time of aortic valvotomy 6 months previously, was found to be occluded, having thrombosed probably shortly after operation. There was a fresh infarct of the left ventricle terminally.

### Case 6

A man of 49 years had two attacks of praecordial pain, 7 and 3 weeks before death. An electrocardiogram showed evidence of an anterior myocardial infarction, and he developed congestive cardiac failure. Infarctectomy was considered and a coronary angiogram was performed. This showed complete

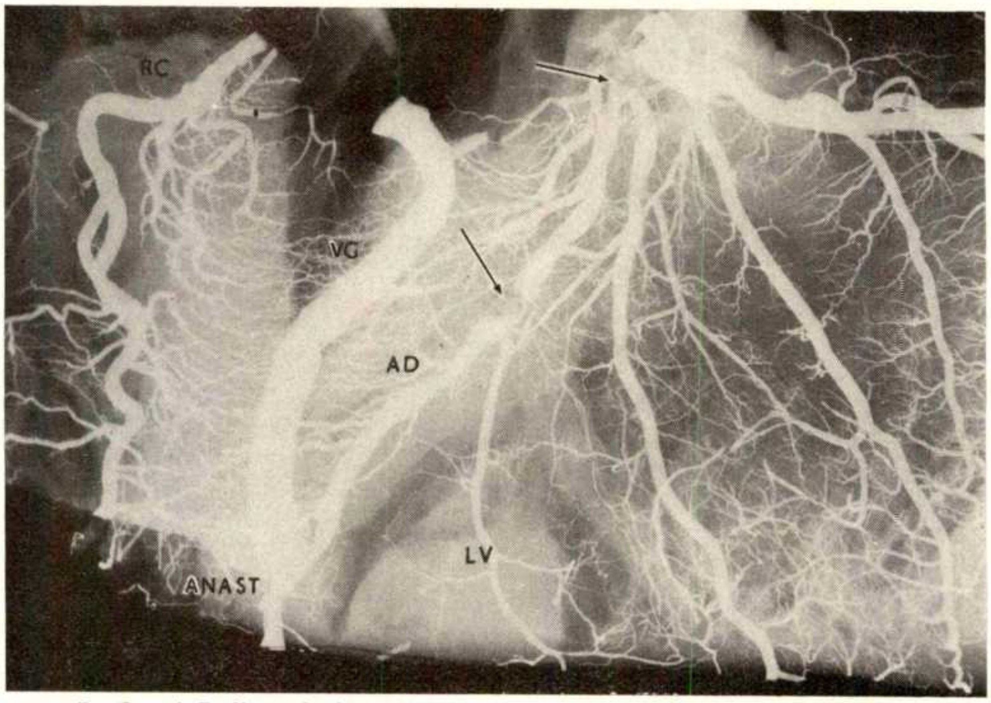

FIG. 7 *Case 6. Radiograph of 'unrolled' heart with right ventricle to left. Vein graft (VG) is patent and supplies left anterior descending artery (AD) which is severely narrowed at 2 sites (arrows) and near anastomosis (ANAST) by continuous thrombus. Infarcted part of left ventricle is poorly vascularized (LV), and shadow of large mural thrombus can be seen.*

occlusion of the left anterior descending coronary artery near its origin, with retrograde filling from the right coronary artery which was also diseased. At operation, a vein graft was inserted into the anterior descending artery, but the infarct was found to be unsuitable for excision. He died 5 days later.

At necropsy the heart weighed 545 g. Medium was injected into the graft and into the left coronary artery. The ostium of the right coronary artery was too narrow to take a thin cannula, but medium appeared from it retrogradely during injection, and it was ligated to raise the pressure within.

Radiographs and dissection showed a dominant left and a small right coronary artery. There was poor vascularization of part of the left ventricle in *x*-ray films (Fig. 7). The ostium and first 3 cm of the right coronary artery were severely narrowed by atheroma to about 1 mm internal diameter. There was a large plaque narrowing the left main coronary artery; the circumflex and posterior descending arteries were only slightly diseased, but the anterior descending artery was severely narrowed by calcified atheroma and a retracting organizing thrombus extended from the origin of the vessel to the graft insertion, leaving the lumen only just patent to medium. Histologically, the thrombus appeared about 2 weeks old; just proximal to the anastomosis it formed a thin band running across the lumen. The vein graft was patent, and so was the distal part of the recipient artery which measured 2 mm in internal diameter. Histologically, the wall of the vein appeared well preserved (Fig. 8) and there was no intimal thickening. The left ventricle showed a combination of extensive fibrous scarring and recent infarction to involve two-thirds of its circumference, including part of the septum. There was a large mural thrombus within the left ventricle. Histologically, one infarct appeared about 2 months old, and the other about 7 to 10 days old.

The only other necropsy finding was an infarct in the right lower lobe of lung, and there were emboli in smaller pulmonary arteries (less than 7 mm in diameter).

**Comment** This patient died 5 days after a vein graft operation for advanced ischaemic heart

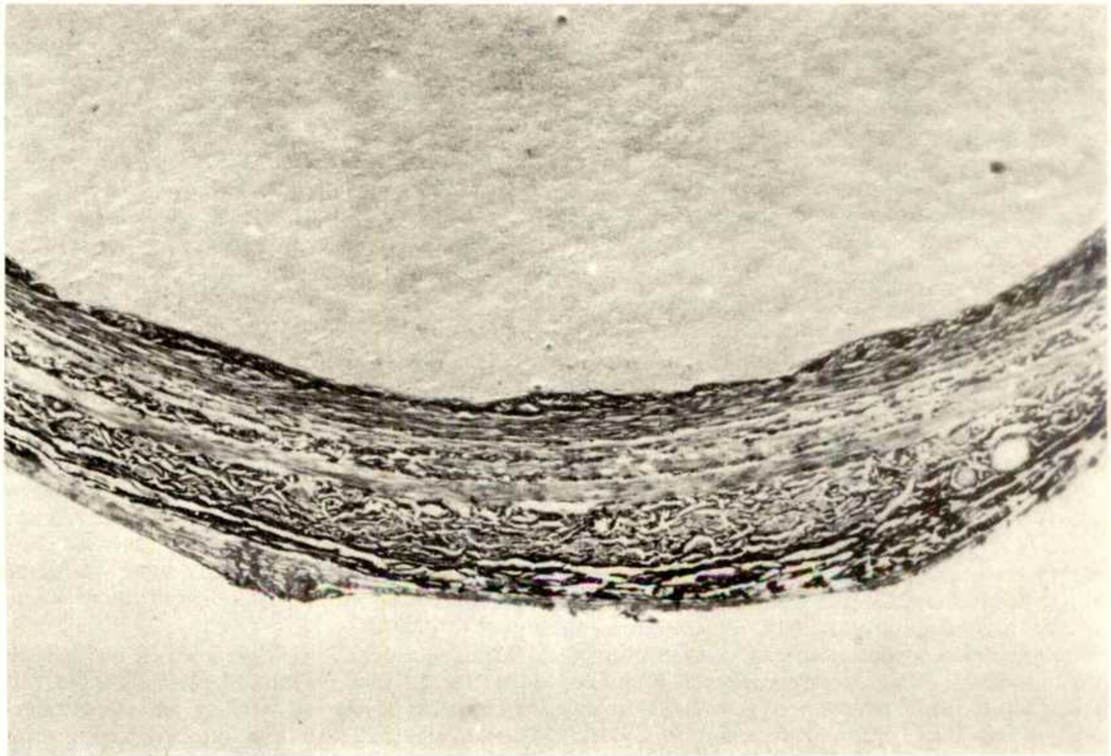

FIG. 8 *Case 6. Transverse section of patent vein graft 5 days after operation. Vessel wall is distended by injection medium seen in upper half of field. The wall appears well preserved. Compare with Fig. 9. (Elastic-van Gieson. ×55.)*

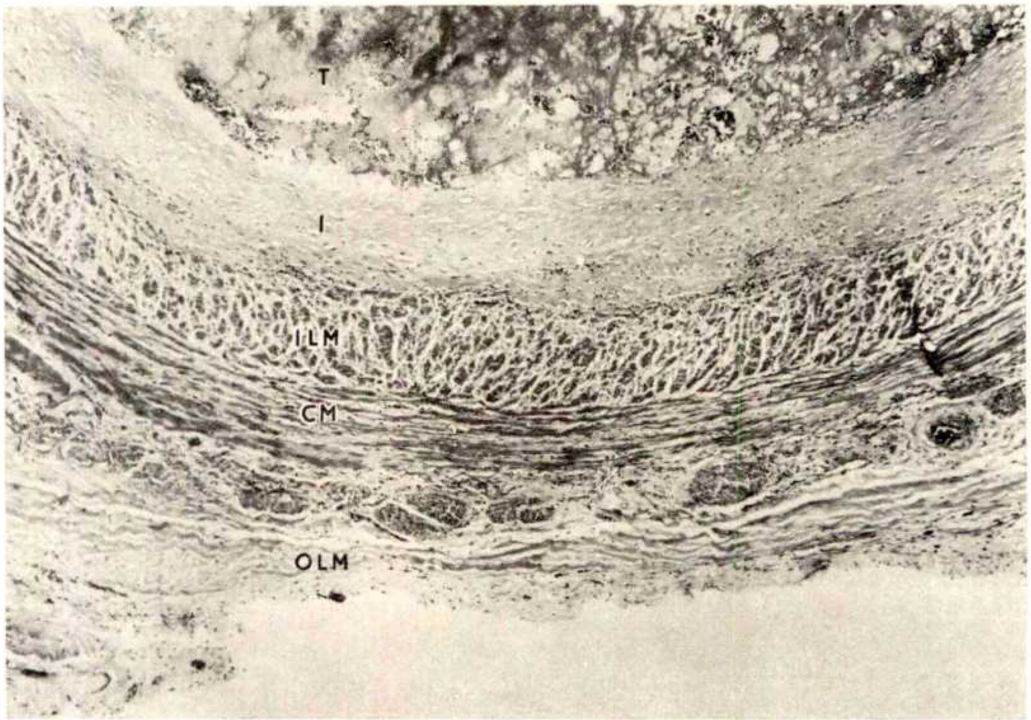

FIG. 9 *Case 7. Transverse section of vein graft from patient who died 13 months after operation. Compared with younger graft in Fig. 8, inner part of wall (I) is thickened by dense collagen and there is recent thrombus in lumen (T). Inner longitudinal (ILM), circular (CM), and interrupted outer longitudinal (OLM) muscle layers of media are well preserved and appear thickened in response to systemic arterial pressure. (H. and E. ×55.)*

disease with cardiac failure; infarctectomy was planned but was not feasible. At necropsy, the vein graft was patent, but about two-thirds of the muscle of the left ventricle and septum were destroyed by infarcts antedating the operation. Small pulmonary emboli were present. The disease of the left ventricle appeared in retrospect to be too extensive to benefit from revascularization.

### Case 7

A man of 60 years had had 6 acute coronary attacks over 17 years and also angina of effort which was latterly very severe. Coronary angiography showed extreme narrowing of the right coronary artery, and at operation a vein graft was inserted distally into this vessel. After operation, he was found to have a hemiplegia which was attributed to an embolus resulting from detachment of mural thrombus from the left ventricle. He died suddenly 13 months after operation.

At necropsy, the heart which was received fixed in formalin was covered by dense postoperative adhesions. The presence of fixed post-mortem blood clot in the coronary arteries precluded the successful use of an injection mass. The walls of the vein graft were thickened and the lumen was blocked by thrombus, which was pale brown proximally and dark reddish-brown distally; the right coronary artery was extremely narrow proximal and distal to the anastomosis. The left main coronary artery was widely patent, but there was severe atherosclerotic narrowing of parts of the anterior descending and circumflex branches. The left ventricle (1·2 cm thick) showed some ischaemic fibrosis high up in the posterior wall; there was no mural thrombus.

Histologically, the vein graft which had been in place for 13 months showed a thick media with hyperplastic layers of circular and longitudinal muscle (Fig. 9). The intima was thickened to about 0·3 mm by dense collagen with widely-spaced fibrocytes that were more numerous away from the lumen. The lumen in proximal sections was filled with fairly recent thrombus, containing degenerat-

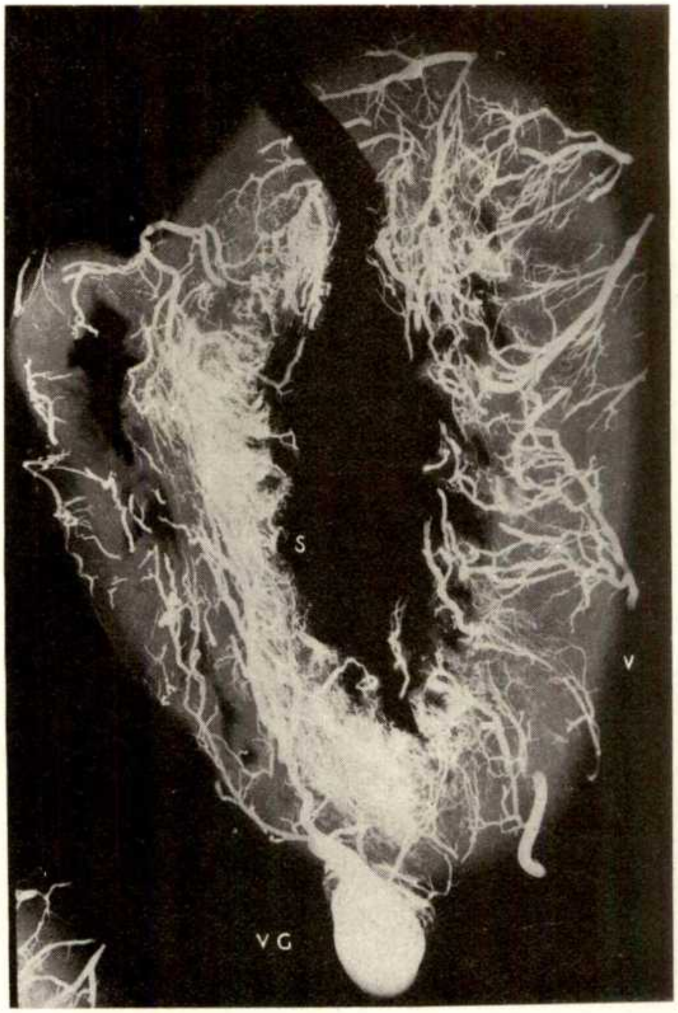

FIG. 10 *Case 8. Radiograph of slice through ventricles showing patent anterior vein graft (VG) communicating with anterior descending artery and branches, including numerous septal anastomoses (S). Slightly deficient filling of vessels in left ventricular wall at V.*

ing red cells and compact fibrin, and becoming organized from the intima. There was a light infiltrate of lymphocytes and plasma cells in a few foci near the junction of adventitia and adjacent adipose tissue. In the intima near the thrombus there were a few foamy phagocytes slightly resembling atheroma, and also some siderotic histiocytes. In the lumen of the graft distally there was more recent thrombus containing intact red cells and showing no signs of organization. Sections of the left ventricle showed ischaemic fibrosis and no evidence of infarction; the HBFP stain was negative.

Other necropsy findings (kindly provided by Dr. H. de C. Baker, Norfolk and Norwich Hospital) included a large old infarct of the left temporal lobe of the brain and oedema of the lungs.

**Comment** This man died 13 months after operation for severe angina. There was severe atherosclerosis of all 3 principal coronary arteries and a vein graft was inserted into the worst affected right coronary artery. At necropsy, the vein graft showed narrowing caused by intimal fibrosis, and blocking of the lumen throughout its length by thrombus of short duration.

### Case 8

A man of 55 years had had angina of effort for 11 years, becoming severe latterly. A coronary angiogram showed severe narrowing of the right coronary artery with retrograde filling of its distal portion from the circumflex artery. There were also severe narrowings of the anterior descending and circumflex branches of the left coronary artery. Vein grafts were inserted into the anterior and posterior descending arteries, but measured blood flow through the grafts was very slow. The left ventricle would not pump effectively, and he died shortly after the operation.

Necropsy showed pulmonary embolism, with complete obstruction of the right main pulmonary artery by a coiled embolus from a leg vein, 12 cm long when unfolded. The heart weighed 365 g, and when medium was injected first into the anterior descending vein graft, it returned from both coronary arteries and from the posterior descending vein graft. The ostia of the coronary arteries were too narrow to inject, and were ligated to maintain pressure during injection of the grafts. Because the aortic end of the posterior descending vein graft was narrow, medium was injected through an incision further down the graft.

Dissection and radiographs confirmed the patency of the grafts. The communication of the vein graft with the anterior descending artery is illustrated in Fig. 10. There was an almost complete atherosclerotic block of the right coronary artery 3·5 cm from the origin. The left main coronary artery was moderately narrowed beyond the stenosed ostium. The lumen of the origin of the anterior descending artery was less than 1 mm in diameter. The circumflex artery was moderately narrowed and a lateral ventricular branch was blocked (Fig. 11) by a haemorrhage into a plaque, confirmed histologically. The posterior vein graft was patent and the recipient posterior descending artery was 2 mm in diameter. The left ventricle was normal in thickness (14 mm) and sections showed ischaemic fibrosis high in the posterior wall. In radiographs there was slightly reduced filling of vessels of the left ventricle (Fig. 10), though sections failed to show infarction and the HBFP stain was negative.

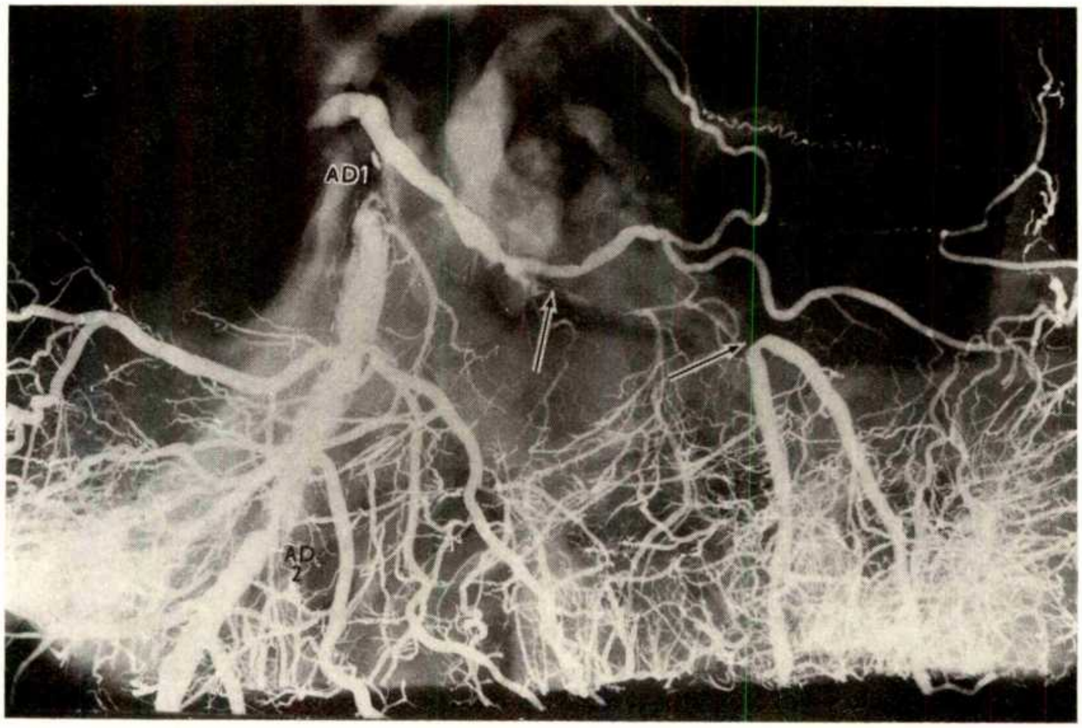

FIG. 11 *Case 8. Radiograph of unfolded left ventricle. Severe atherosclerotic narrowing of anterior descending branch of left coronary artery in 2 sites (AD 1, AD 2). Large lateral branch of circumflex artery is blocked (between arrows) by haemorrhage into a plaque.*

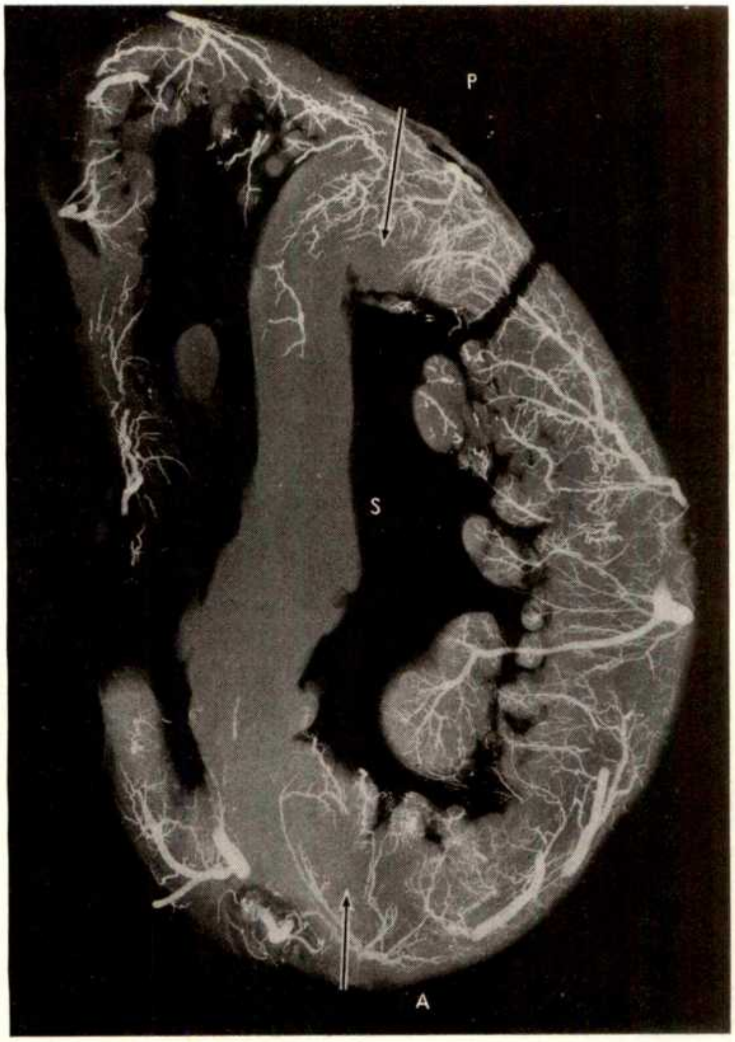

FIG. 12 *Case 9. Radiograph of slice of ventricles. Infarction (between arrows) of interventricular septum (S) is accompanied by almost completely deficient filling of vessels of most of septum and part of anterior (A) and posterior (P) walls of left ventricle.*

**Comment** This patient died from massive pulmonary embolism occurring during a vein graft operation. He was operated on for angina of long duration, latterly disabling. There was severe narrowing of the ostia and other parts of both coronary arteries and also a haemorrhage into a plaque on the circumflex artery. The vein grafts were patent.

## Case 9

A man of 41 years, with gout for 18 years, had had 2 attacks of myocardial infarction 13 and 2 months before death. Heart block followed the second illness. Coronary angiography showed occlusion of the anterior descending artery, and a major stenosis of the right coronary artery. A large part of the left ventricle was non-contractile. Operation was undertaken for excision of an aneurysm of the left ventricle, and a vein graft was put into the right coronary artery. He did not recover from the operation.

At necropsy, the heart weighed 475 g. Medium injected into the patent vein graft returned from the narrowed orifice of the right coronary artery, which was then ligated. The left coronary artery was also injected.

Dissection, radiographs, and histology showed narrowing of the lumen of the right coronary to 1 mm internal diameter at a point 3 cm from its origin (beyond the ligation), and also narrowing to 2 × 1 mm distal to the graft insertion, with widening later. The left main coronary artery was moderately narrowed; the anterior descending artery was blocked by a haemorrhage into a plaque and new thrombus filling the small remaining lumen. The middle region of the circumflex artery was narrowed by atherosclerosis and blocked by an organizing thrombus. The interventricular septum showed extensive conspicuous yellow infarction of fairly recent occurrence, and there was fibrosis of the anterior and posterior walls (aneurysm excised), and other parts of the septum. There were small patches of ischaemic fibrosis in the right ventricle. The post-mortem angiograms showed almost complete absence of vessel filling in the infarcted septum and in parts of the anterior and posterior walls of the left ventricle (Fig. 12).

Other findings at necropsy were gouty deposits in a metatarsophalangeal joint, and infarcts in the right lung and right kidney.

**Comment** The great severity of the coronary artery disease and the resulting damage to the left ventricle were well appreciated before operation, but it was considered that vein grafting and aneurysmectomy offered the only hope for this relatively young patient. He did not recover from the operation. Pathologically, it was thought in retrospect that too much of the left ventricle had been destroyed before operation for benefit to result from surgery.

### Case 10

A man of 51 years had had angina on exercise for 2 years and a myocardial infarct 9 months before death. Coronary angiography showed severe atherosclerosis of the right main coronary artery and of the origins of the anterior descending and circumflex branches of the left coronary artery. Vein grafts were inserted into the anterior and posterior de-

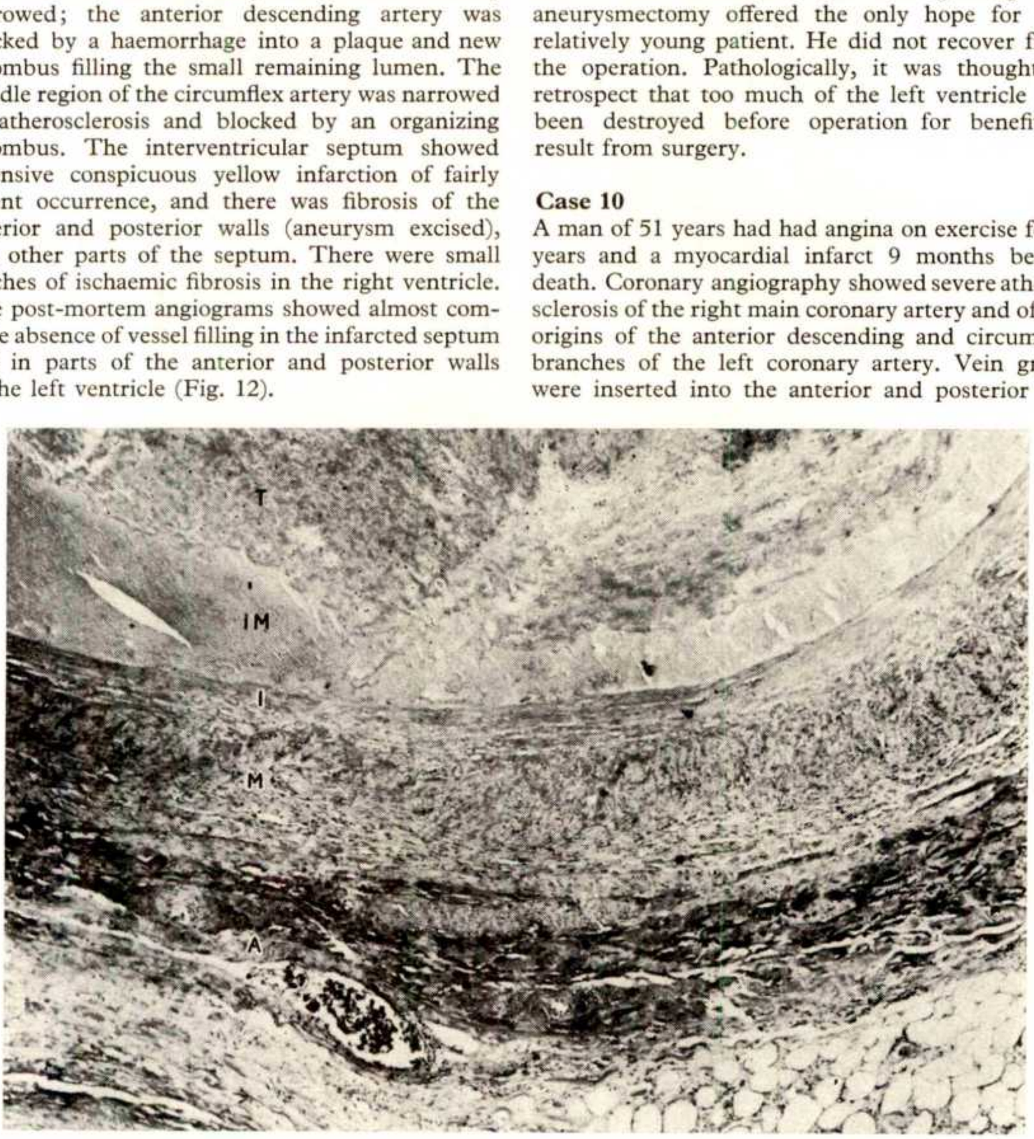

FIG. 13 *Case 10. Transverse histological section of vein graft to posterior descending artery near anastomoses with that vessel. Thrombus (T) and small amount of injection mass (IM) in the lumen. Intima (I) shows mild fibrous thickening (2½ weeks after operation) and media (M) is also thickened (compare with the 5-day graft in Fig. 8). Suture material in adventitia at A. (Elastic-van Gieson. ×55.)*

scending coronaries. Two and a half weeks later when recovery appeared well advanced, he suddenly collapsed and died from pulmonary embolism despite surgical embolectomy.

At necropsy, the heart weighed 585 g. Medium injected into both coronary arteries returned slowly up the anterior vein graft, but not at all up the posterior graft. The aortic ends of both grafts were very narrow and could not be probed, though the corresponding openings in the aortic wall were wide.

Dissection, radiographs, and histology confirmed the patency of the anterior descending vein graft, but the graft to the posterior descending artery was blocked by an organizing thrombus stretching from the aortic and almost to the coronary end (Fig. 13). The recipient posterior descending artery was patent and measured 2 mm in internal diameter proximal to the anastomosis, and 1 mm distally. The right coronary artery showed moderate atherosclerosis and calcification. The left main coronary artery and its circumflex branch were similarly affected. The worst disease was in the anterior descending artery, which was not only thickened by intimal fibrosis and calcification, but almost completely blocked by a large haemorrhage into a plaque, accompanied by a small thrombus in the lumen. The vessel also contained a small amount of thrombus near the anastomosis, where it measured 2 mm in internal diameter, both proximal and distal to the anastomosis.

The left ventricle showed the anteroseptal infarct, nine months old. In the lungs there were very many emboli blocking medium-sized pulmonary arteries. Dissection of both femoral veins revealed many similar small thrombi.

**Comment** The patient died of pulmonary embolism two and a half weeks after a vein graft operation. There were thrombi in both femoral veins (not confined to the left leg from which the grafting vein had been taken). A vein graft to the anterior descending artery was patent. The recipient vessel showed a haemorrhage into a plaque proximally, plus thrombosis, and there was an anteroseptal infarct. A vein graft to the posterior descending artery seemed to have become blocked by thrombus soon after the operation, possibly because of a narrow aortic anastomosis.

## Discussion

This pathological study indicates that death in 10 cases of severe coronary atherosclerosis occurring during early experience with aortocoronary saphenous vein bypass grafting was usually caused by the extreme severity of the coronary artery disease, and of its effects on the left ventricle. The 10 deaths occurred during a period when approximately 80 vein-grafting operations were performed, representing a mortality rate of 12·5 per cent, with a follow-up period of up to 13 months after operation. This high mortality in these early cases, compared with our own later experience (Balcon *et al.*, 1974) and that of others, may be partly the result of the severity of coronary atherosclerosis.

The ostium of the left main coronary artery was severely stenosed in 3 of the 10 cases reported here. The left anterior descending artery was severely stenosed or occluded in 9 cases. The circumflex artery showed severe stenosis or occlusion in 6 cases. The right coronary artery showed stenosis of the orifice in 7 cases and the main vessel was severely stenosed or occluded in 7 cases. The posterior descending artery was severely stenosed in 2 cases.

This very advanced coronary atherosclerosis defeated the operation in several ways. If the left ventricle was severely damaged by ischaemia before operation, there was sometimes too little intact muscle remaining for the patient to benefit from vein grafting or even to allow him to survive the operation. It is well recognized that necropsies commonly show more extensive myocardial infarction than is suspected during life (Edwards, 1971). It is reasonable to expect that vein grafting will improve the function of surviving muscle fibres and reduce the chances of further ischaemic necrosis, but significant regeneration of muscle fibres is unlikely to occur. Extensive left ventricular damage is detectable in life by ventricular angiography and by measuring the end-diastolic pressure. A higher operative mortality rate is well recognized when the latter is raised (Cooley *et al.*, 1973); a ventricular ejection fraction of less than 40 per cent may be used as a contraindication to surgery (Collins *et al.*, 1973). A non-invasive method for demonstrating the state of perfusion of the heart is now available using $^{43}$K injected into a peripheral vein and measurement of myocardial uptake (Botti and MacIntyre, 1974). Studies of the pathology of patients dying of cardiogenic shock (without operation) have revealed infarction of more than 40 per cent of the left ventricle (Bouch and Montgomery, 1970; Bolooki *et al.*, 1971; Mundth *et al.*, 1971; Page *et al.*, 1971). In the present 10 cases, the left ventricle was affected in all, with ischaemic fibrosis in 8 cases and recent infarction in the other 2 cases. There was a fibrous aneurysm of the ventricle (resected) in 2 cases and ischaemic scarring of the posterior wall in 7 cases, anterior wall in 3 cases, lateral wall in 3 cases, and septum in 4 cases.

Severe disease of small coronary arteries proximal or distal to the site of graft insertion may reduce blood flow in either direction. One result may be graft thrombosis. Proximal occlusion of a coronary artery may sometimes cause infarction of that part of the ventricle which was dependent upon retrograde flow from a graft (Case 6). Worsening of atherosclerosis of coronary arteries proximal to grafts, more severe than in non-grafted vessels, has been well documented in studies with pre- and postoperative coronary angiograms (Aldridge and Trimble, 1971; Bousvaros, Chaudry, and Piracha, 1972; Malinow *et al.*, 1973; Diethrich and Prian, 1973). Experimentally, it has been shown that blood flow is reduced by about 50 per cent in a coronary artery proximal to a graft; flow in a stenosed coronary artery proximal to a graft is decreased even more (Kakos *et al.*, 1972). The resulting stasis encourages thrombosis which in turn contributes to the formation of more atherosclerotic thickening (Duguid, 1946; Heard, 1949). Another reason for proximal deterioration may be probing during the operation. This was thought to be the explanation for the haemorrhage into the atherosclerotic anterior descending artery proximal to the anastomosis in Cases 9 and 10. Spontaneous haemorrhage in coronary plaques has been reviewed by Friedman (1970).

A practical problem observed in the present study and not sufficiently widely appreciated, results from severe atherosclerotic narrowing of coronary ostia. The ostium of the right coronary artery was severely narrowed in 7 out of 10 of the present cases, and of the left in 3 cases. Ostial narrowing may jeopardize the blood supply to the myocardium in two practical circumstances, viz. by causing gripping of the catheter during coronary angiography, and by interfering with, or preventing, coronary artery cannulation and perfusion during an accompanying aortic valve replacement procedure. Ventricular fibrillation and myocardial infarction have been recorded after coronary arteriography (Sones and Shirey, 1962; Gau *et al.*, 1970; and the present Case 1). It has been suggested that the Judkins type of catheter (Judkins, 1967) may be associated with this problem more than other types, perhaps because of its extra efficiency in seeking out and entering the narrowed coronary ostia. The difficulty of perfusing narrow coronary ostia at operation has been discussed by Effler and co-workers (1967).

A higher mortality has been reported when it has been necessary to operate on heart valves or ventricular aneurysms at the same time as inserting vein grafts (Heimbecker *et al.*, 1967; Kay *et al.*, 1970, 1972; Danielson, Gau, and Davis, 1973; Cooley *et al.*, 1973). Three of the present cases were in this category (Cases 2, 3, and 5). The main reason for the higher mortality in such patients may be the poor condition of the left ventricle before operation.

Death was caused by pulmonary embolism in 2 cases. This occurred during the operation in Case 8, and 2½ weeks later in Case 10. Pulmonary infarcts were also found at necropsy in Cases 6 and 9. While pulmonary embolism might be expected to occur very commonly in bypass graft patients, as a result of the presence of predisposing factors such as heart disease, postoperative hypercoagulability, and operation on leg veins, further experience suggests that there may not be an especially high incidence of fatal embolism in these patients (S. Lennox, 1974, personal communication).

Cerebral damage (Cases 4 and 7) is a well-recognized complication of heart surgery though far less common now than formerly. Some kind of cerebral disturbance at 3 days after open heart surgery was reported by Branthwaite (1972) in 19·2 per cent of her patients, especially in the older age-group, but was usually transient. The mortality was 2 per cent. In 1973, the incidence of cerebral disturbance was lower, at 7·4 per cent (Branthwaite, 1975). Prophylactic measures to eliminate microemboli and minimize the risks of hypotension and hypothermic circulatory arrest were thought collectively beneficial. There are many particles in the pump return line (Solis *et al.*, 1974).

## Graft patency

Ten of the 14 vein grafts inserted in the present series, i.e. 71 per cent, were still patent at the time of death. The other 4 were occluded by fresh or organizing thrombus. The 14 vein grafts were inserted into the following vessels (number of patent grafts in brackets): anterior descending 5 (4), circumflex 1 (1), right 5 (3), and posterior descending 3 (2) (see Table). A similar patency rate has been reported by others in necropsy material (Marti, Bouchardy, and Cox, 1971; Lespérance *et al.*, 1972; Ross *et al.*, 1972). Some of the patients in the present series died very shortly after operation, and there was thus evidence only of short-term patency. In a recent necropsy study, Vlodaver and Edwards (1973) found that only 3 out of 16 grafts (18·75%), which had been in place for 2 months or longer, were still patent. However, evidence obtained from patients restudied in life gives a truer and more hopeful picture (Ross *et al.*, 1972; Gott, 1974; Bourassa *et al.*, 1972). It has been found that at one year, the patency rate is 65 to 75 per cent but the occlusion rate in later years appears to be only about 5 per cent per annum (*British Medical Journal,* 1974). Hammond and

TABLE *Summary of operations and necropsy findings*

| *Case No.* | *Indication for operation* | *Operation* | *Cause of death* | *State of grafts at necropsy* | *Survival time* |
|---|---|---|---|---|---|
| 1 | Angina | Vein grafts to AD and PD | Myocardial infarction | Patent | Nil |
| 2 | Angina | AV replacement; vein graft to AD | Thrombosis of RC and of graft to AD | Thrombosed | 8 d |
| 3 | LV aneurysm | Aneurysm LV resected; vein graft to RC | Ischaemic fibrosis LV | Patent | 3 wk |
| 4 | Angina | Vein grafts to RC and C | Cerebral softening | Patent | 10 d |
| 5 | Angina | Aortic valvotomy; vein graft to RC | Severe coronary artery atherosclerosis; recent myocardial infarction; calcific aortic valve disease | Thrombosed (shortly after operation) | 6 mth |
| 6 | Aneurysmectomy considered | Vein graft to AD (no aneurysmectomy) | Ischaemic destruction much of LV (old and recent infarcts) | Patent | 5 d |
| 7 | Angina | Vein graft to RC | Thrombosis of graft; severe coronary artery disease | Thrombosis (recent) and intimal fibrosis | 13 mth |
| 8 | Angina | Vein grafts to AD and PD | Pulmonary embolism during operation | Patent | Nil |
| 9 | LV aneurysm | Aneurysm LV resected; vein graft to RC | Ischaemic destruction of much of LV (old and recent infarcts) | Patent | Nil |
| 10 | Angina | Vein grafts to AD and PD | Pulmonary embolism (2½ weeks after operation) | Patent to AD; thrombosed to PD | 2½ wk |

Abbreviations: AD=anterior descending artery, AV=aortic valve, C=circumflex artery, LV=left ventricle, PD=posterior descending artery, RC=right coronary artery.

Poirier (1973) and Flemma *et al.* (1972) reported patency rates of over 80 per cent. Reul and co-workers (1972) demonstrated angiographically patency of a vein graft that had been functioning for 7 years.

Early occlusion of vein grafts is usually a result of thrombus forming in the lumen when the flow is slow. Graft blood flow readings obtained at operation ideally should be in the region of 80 to 100 ml/min (Favaloro *et al.*, 1970). It has been shown clearly that there is a fall in patency rate with flows of less than 40 ml/min (Walker *et al.*, 1971). Occlusion has been found in more than 75 per cent of grafts with flow rates below 25 ml/min (Grondin *et al.*, 1971a, b, c, d, e). Stagnation and occlusion are usually thought to be caused by coronary artery disease above and/or below the level of the graft insertion, but a tight anastomosis at either end of the graft may also be responsible (Bouch *et al.*, 1972). The resulting occlusion may be of two sorts, a laminated thrombus formed initially in a moving blood stream and/or a blood clot formed in a still column of blood after the lumen has become occluded by thrombus. Early occlusion may also result from changes in the endothelium encouraging thrombosis. Experimental studies have shown mural thrombi in vein grafts during the first week, clearing later when the endothelium is restored (Brody, Angell, and Kosek, 1972a). The endothelial changes may be linked with partial necrosis of the media, and some of the intimal thickening may be of proliferating muscle cells as identified by electron microscopy (Kern, Dermer, and Lindesmith, 1972). Medial fibrosis has also been observed.

Occlusion of a vein graft some months after operation usually seems to be the result of thickening of the intima. Thrombus may eventually occur in an occluded, thickened vein, as in Case 7. It is possible that worsening of atherosclerosis in coronary arteries distal to a graft slows blood flow in the graft, and causes mural thrombosis; subsequent organization of thrombi would contribute to intimal fibrosis, as has been demonstrated in atherosclerosis (Duguid, 1946; Heard, 1949). Fibrous intimal changes have been described in vein grafts in leg arteries (DeWeese *et al.*, 1966; DeWeese and Robb, 1971). In coronary grafts, fibroblasts proliferate in a basophilic mucoid matrix containing acid mucopolysaccharides (Vlodaver and Edwards, 1971). Intimal thickening has been observed as early as 10 days after operation (Marti *et al.*, 1971) and is very common, occurring in one series in 6 out of 8 grafts examined 3½ to 9 months after operation (Aldridge and Trimble, 1971). About 5 per cent of veins may show intimal thickening at the time of insertion (Flemma *et al.*, 1972). In comparing the intimal thicknesses of veins pathologically it is important to ensure that they have been fixed in comparable conditions of distension, because the intima appears thicker in a relaxed than in a distended vein. Since the grafted veins in the present study were injected under a standard pressure with the gelatin-containing mass, and fixed distended, comparisons were justifiable.

Intimal thickening may be a problem in long-term survivors and has been studied pathologically by Johnson *et al.* (1970a, b), Grondin *et al.* (1971a, b, c, d, e), Marti *et al.* (1971), and Vlodaver and Edwards (1971, 1973). The cause of the intimal thickening is not known at present but there are several possibilities. One suggestion is that trauma and irrigating solutions play a part (Flemma *et al.*, 1972). Another is that the natural adventitial vessels are cut when the vein is transplanted so that the vein wall becomes ischaemic (Brody *et al.*, 1972a; Brody, Kosek, and Angell, 1972b). A third factor suggested is the greater intraluminal pressure in a vein transplanted into an arterial circuit; haemodynamic stress is probably of great importance (Bourassa *et al.*, 1972; Kern *et al.*, 1972; Vlodaver and Edwards, 1973). The intima of a vein exposed to arterial pressures may react by proliferating. Fourthly, a less likely explanation is that the vein becomes atherosclerotic. Some authors have found lipid present after 18 months (Effler *et al.*, 1971), but most evidence does not support this explanation. Atherosclerotic changes are uncommon in vein grafts in leg arteries (Downs, 1971).

More time and experience will be necessary before the importance of intimal thickening as a potential limiting factor in the usefulness of coronary vein grafts can be firmly established. Vlodaver and Edwards (1973) studied 86 coronary vein grafts in 53 necropsies and found obstruction in 30 grafts. Grafts occluding during the first month were thrombosed, but in those occluding later (up to 3½ years) fibrous intimal proliferation was more important than thrombosis as a cause of occlusion. In the present study, conspicuous intimal fibrosis was seen in Case 7 where the graft had been patent for about 13 months before finally becoming occluded by thrombus. Three other grafts thrombosed shortly after operation, before intimal fibrosis could take place. Flemma and co-workers (1972) illustrated a section of a thickened vein patent at 3 years. The incidence of occlusion of grafts is, however, not fairly portrayed in necropsy series. Vein grafts in atherosclerotic limb arteries are often found to be still patent when death occurs from some other cause.

Dilatation is not a problem with these grafts but localized stenosis certainly is. Bourassa and co-workers (1972) found localized stenoses, sometimes severe, in 27 out of 124 vein grafts on repeat coronary cineangiography. Seventy per cent were in the proximal third and 30 per cent in the distal third. Hammond and Poirier (1973) found stenoses in 9 per cent of their cases. Stenosis may develop at the sites of anastomosis at each end of the graft; this was a complication reported when the aorta was merely slit transversely before making the anastomosis; a transverse cut tends to close whereas a vertical cut tends to open. Best results follow removal of a small piece of aorta. Stenoses may develop along the course of the graft when venous valves open as a result of turbulence (Diethrich and Prian, 1973) with resulting formation at these sites of thrombus which organizes to become a fibrous obstruction. Valve cusp fibrosis is a recognized obstructive lesion in vein grafts in leg arteries and may require local excision (Downs, 1971).

## Comments on pathological technique

In general, the method of injecting a warmed gelatinous mass directly into the warmed heart using tied-in coronary cannulae was satisfactory for the present purpose. The quality of fixation suffered to some extent from the effects of freezing and thawing for storage (Heard, 1955a, b), exposure to hot water in the unfixed state, and post-mortem autolysis. The use of a medium which could be used at room temperature would probably be better for the preservation of histological detail (Schlesinger, 1957). However, the present technique was so successful in filling the vessels required that once started it was not changed. The sizes of vessels filled were ideal for this particular study, and the results were comparable with those obtained by previous workers (Gross, 1921; Schlesinger, 1938, 1957; Harrison and Wood, 1949; Schwartz and Mitchell, 1962; Fulton, 1965). To study finer vessels, a different injection mass and different radiological equipment and films are necessary (Farrer-Brown and Rowles, 1969). For the present study, injecting smaller vessels would have produced a fine haze which would have obscured the large and medium sized vessels.

At the beginning of this project, a trial was made of a specially-constructed catheter consisting of a balloon which was inflated below the aortic valve, and a rubber bung tied into the ascending aorta (Rissanen, 1970). The mass was injected into the intervening ascending aorta and thus into the coronary arteries. Aortic root injection for coronary arteries (Baroldi and Scomazzoni, 1967) has been recommended by the World Health Organization (1970). Present experience by the author does not support that recommendation. When the mass solidifies and is fixed by formalin in the aorta, it interferes with radiological views of the coronary arteries in whole hearts despite careful orientation, and also with subsequent dissection and radiography of the 'unrolled' specimen. The aortic valve region is distorted by the presence and upward pull of the balloon, and, also, medium commonly leaks past the balloon down into the left ventricle, wasting medium and spoiling radiographs. The only possible disadvantage of cannulating the coronaries directly as in the present study, was that the ostia were not visualized radiologically, but this was no problem because they could be examined perfectly well by the naked eye at the time of cannulation.

## Concluding remarks

Johnson and his colleagues (1969) thought that no patient should be refused treatment because of the extent of the coronary disease. The present study emphasizes that the pathological changes in the ischaemic left ventricle are sometimes too severe for vein grafting to improve left ventricular function (Bolooki and Jude, 1972; Diethrich and Prian, 1973; Balcon *et al.*, 1974; Danielson *et al.*, 1973; Spencer *et al.*, 1971). The present study also shows that, if left ventricular function is reasonably satisfactory despite extensive severe coronary artery disease, more radical coronary surgery is needed—endarterectomy and multiple vein grafts—to achieve good results. In this early series, 6 of the 10 patients who died received only one graft.

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# Endomyocardial fibrosis associated with daunorubicin therapy

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*A case of endomyocardial fibrosis in a patient with acute myeloblastic leukaemia treated by daunorubicin is reported. The pathological findings are indistinguishable from tropical endomyocardial fibrosis.*

Endomyocardial fibrosis has a well-defined geographical distribution, most reported cases occurring among the indigenous tribes of East and West Africa (Shaper, 1970). The disease has been described in Europeans living in Africa (Brockington, Olsen, and Goodwin, 1967) but in most of these there was some evidence of filariasis and eosinophilia was usually present. Eosinophilia is also seen in Loeffler's endocarditis, a non-tropical disease which has macroscopical features identical to those seen in tropical endomyocardial fibrosis (Roberts, Liegler, and Carbone, 1969). In eosinophilic leukaemia a cardiac lesion indistinguishable from endomyocardial fibrosis has been described (Odeberg, 1965). We report here the finding of severe endomyocardial fibrosis in a young woman dying from acute myeloblastic leukaemia and who received prolonged therapy with daunorubicin, a powerful cytotoxic agent known to be cardiotoxic.

## Case report

In February 1973 a 21-year-old student presented with a two-month history of progressive tiredness, bruising, and upper respiratory tract infections. At the age of 18 months she had developed a hypoplastic anaemia following sulphonamide therapy for upper respiratory tract infection.

On examination she was found to be anaemic with purpura and ecchymoses. There was no lymphadenopathy or hepatosplenomegaly. The heart was normal clinically. The peripheral blood count showed: haemoglobin 6·9 g/dl, white cell count 52 000/mm$^3$, with 75 per cent blasts and platelets 16 000/mm$^3$. The bone-marrow confirmed acute myeloblastic leukaemia.

Clinical and haematological remission was induced with daunorubicin and cytosine arabinoside (M.R.C. Leukaemia Trial, Barts III induction programme). After eight courses she was maintained on a monthly regimen of daunorubicin and cytosine arabinoside alternating with thioguanine and cytosine arabinoside (M.R.C. Leukaemia Trial, Barts III remission programme).

In January 1974, having received a total dose of 880 mg daunorubicin (550 mg/m$^2$ body surface area), she complained of increasing dyspnoea and was found to be in heart failure, with clinical evidence of cardiac tamponade. An echocardiogram confirmed the pericardial effusion; the electrocardiogram showed sinus rhythm, low voltage complexes, and flattening of the T waves in the chest leads. She responded well to digoxin and diuretics, and repeat echocardiograms showed progressive reduction in the size of the effusion. She continued to have clinical evidence of heart failure, with a triple rhythm and tachycardia, but was well enough to return to her college. Daunorubicin was withdrawn and she remained in haematological remission on monthly five-day courses of thioguanine, cytosine arabinoside, and prednisolone. After a further five months her leukaemia relapsed and despite an intensive course of cytotherapy with a combination of thioguanine, cytosine arabinoside, methotrexate, prednisolone, cyclophosphamide, and vincristine, remission was never again achieved. In December 1974 she was readmitted with systemic candidiasis and intractable heart failure and died a week later. An echocardiogram was suggestive of a thickened myocardium and there were no new changes on the electrocardiogram.

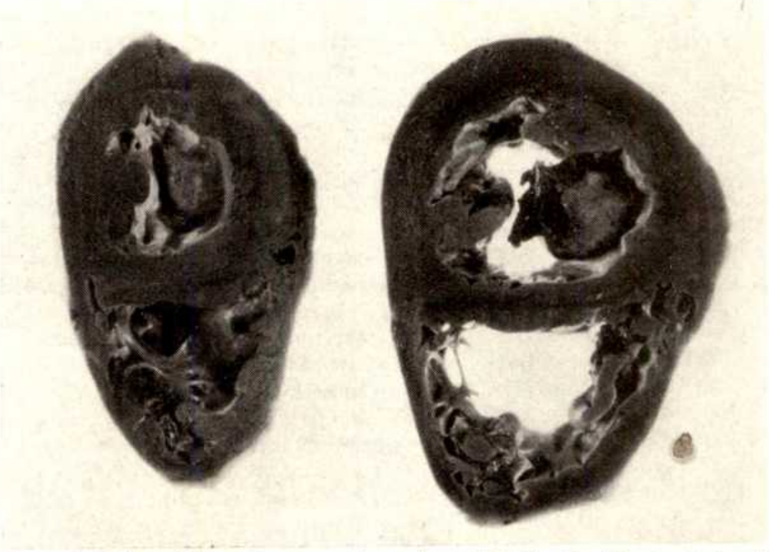

FIG. 1 *Two apical slices of heart demonstrating endocardial fibrosis with superimposed thrombus.*

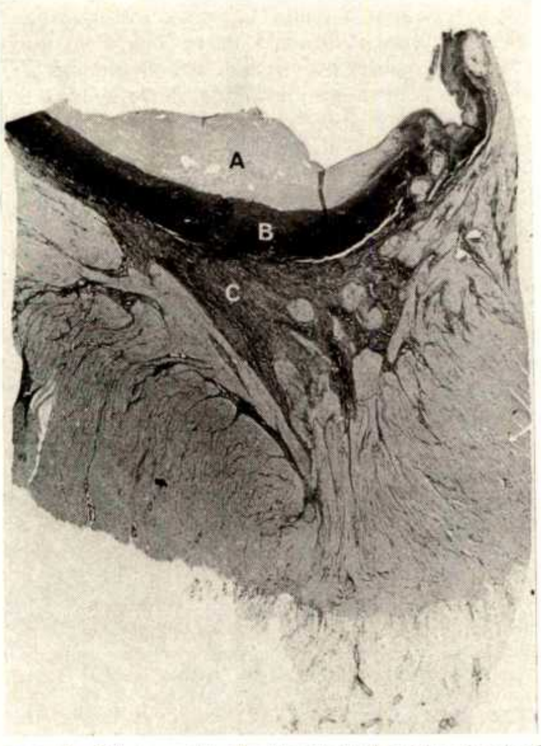

FIG. 2 *Photograph of a histological section (stained with elastic van Gieson) of the left ventricular wall. Thrombus (A) is seen overlying the endocardial fibrosis (B), fibrosis. (C) Fibrosis extends into the underlying myocardium.*

## Necropsy

The body was that of a thin, young woman (weight 59 kg, height 173 cm). The necropsy was limited to an examination of the thoracic and abdominal viscera. All the internal organs were pale, there was a mild hepatosplenomegaly (liver weight 1970 g; spleen weight 280 g) but otherwise no macroscopical abnormality was seen in the abdominal viscera. The significant findings were in the chest, both lungs being oedematous (right lung 950 g; left lung 600 g). 70 ml clear straw-coloured fluid were present in the pericardial cavity and the heart was enlarged, weighing 500 g. Both chambers of the heart were slightly dilated (mitral valve circumference 11 cm, tricuspid valve circumference 13 cm). Fibrous thickening of the endocardium was present in both ventricles. On the right the fibrosis was confined to the apical region producing endocardial thickening of up to 0·1 cm. In the left ventricle the endocardial fibrosis was most obvious at the apex where it reached a thickness of 0·3 cm; however it rapidly diminished away from the apical region, the papillary muscles, chordae tendineae, and valves being uninvolved. A 3 cm mass of thrombus was superimposed on the apical fibrosis in the left ventricle (Fig. 1). Histological sections of the heart showed that the endocardial thickening was a result of the deposition of mature collagen, upon which thrombus was superimposed (Fig. 2). The deeper layers of the thickened endocardium showed a conspicuous vascularity with numerous small capillary blood vessels. This vascular fibrous tissue extended irregularly into the inner third of the underlying myocardium and was associated with a heavy deposition of haemosiderin. In addition to the associated chronic inflammatory infiltrate, occasional primitive cells of the myeloid series were seen. The myocardium away from the scarred areas showed dilated capillary blood vessels and an increase in interstitial connective tissue but no other significant abnormality. Histological sections of other organs confirmed the macroscopical findings and many organs were infiltrated by leukaemic cells. The bone-marrow was hypercellular and replaced by primitive myeloid cells.

## Discussion

The cardiotoxic effects of daunorubicin have been known since the first clinical trials (Tan *et al.*, 1967; Macrez *et al.*, 1967). The usual clinical features are tachycardia, hypotension, and intractable heart failure. These effects appear to be dose-related in children but not in adults, where they may be quite abrupt in onset, with few specific warning signs. Serial electrocardiograms during therapy may show arrhythmias, depression of the ST segments, and T wave inversion, which are more frequent in the elderly (Toghill *et al.*, 1971). Cardiotoxicity usually appears after at least three months of therapy and within one hundred days of the last dose (Halazun *et al.*, 1974). Malpas and Scott (1969) warned against using daunorubicin in continuous high dosage and reported three patients who developed cardiotoxicity after having received less than 300 mg of the drug. It has been estimated that approximately 10 per cent of patients receiving daunorubicin die as a result of cardiotoxicity (*British Medical Journal,* 1967). The other two maintenance drugs used in this patient, cytosine arabinoside and thioguanine, have not been described as being cardiotoxic, either administered alone or in combination (D. A. G. Galton, 1975, personal communication).

The structural changes induced in the heart by daunorubicin were first reported by Ripault, Weil, and Jacquillat (1967) and included patchy myocardial degeneration and fibrosis and intraventricular thrombosis. More recent studies by Buja *et al.* (1973) have confirmed these findings and related the severity of damage to the total dose of daunorubicin received. In our patient the heart showed all these features, with extensive myocardial fibrosis extending through the inner third. The distribution of the cardiac damage and the presence of haemosiderin are difficult to explain. There was no infiltration by eosinophils.

Endomyocardial fibrosis is endemic in several tropical countries affecting the indigenous population (Davies, 1948) as well as Europeans who have lived there for some time (Brockington *et al.*, 1967). It usually begins as a non-specific febrile illness merging eventually into congestive cardiac failure. Morphologically there is fibrosis of the inflow tract and at the apex of one or both ventricles. This reduces the elasticity of the heart and, if the chordae tendineae are involved, causes regurgitation of the atrioventricular valves. There is commonly a pericarditis without constriction. In early cases the endocardial lesions are covered by thrombus but in chronic cases thrombus is rarely seen. The cause is unknown but studies have focused on an immunological disorder, and hypersensitivity reactions to streptococcus (Abrahams, 1959), filaria (Ive *et al.*, 1967), and malaria (Shaper *et al.*, 1967) have been suggested. A similar condition was described by Löffler (1936) in two Europeans with non-tropical endomyocardial fibrosis and striking eosinophilia. Morphologically and histologically tropical endomyocardial fibrosis and Löeffler's fibroplastic endocarditis are indistinguishable, apart from the comparative lack of superficial thrombus in the former (Brockington and Olsen, 1972). Eosinophilia is pronounced in Loeffler's endocarditis (average 32 000/mm$^3$), compared with endomyocardial fibrosis in Europeans resident in Africa (average 7000/mm$^3$) and tropical endomyocardial fibrosis (average 685/mm$^3$). Furthermore, some 40 per cent of patients with eosinophilic leukaemia are said to develop endomyocardial fibrosis indistinguishable from the types mentioned above (Odeberg, 1965).

It is possible, therefore, that endomyocardial fibrosis may be the end result of a variety of initiating factors linked in some way by an altered reaction to various toxins or allergens. In West Africa and in Europeans living in the tropics this factor may be parasitic or bacterial. In other instances the presence of eosinophilia suggests a hypersensitivity state. Indeed, the possibility of eosinophils themselves being cardiopathic cannot be ignored (Brockington, Luzzato, and Osunkoya, 1970). As far as daunorubicin cardiotoxicity is concerned eosinophilia has not been reported and it was not seen in our patient, whereas the morphology and histology of the heart was identical with endomyocardial fibrosis. The absence of cardiotoxicity with anti-leukaemic treatment regimens not incorporating daunorubicin suggests that this drug has a direct toxic effect upon the heart (Smith, 1969) and we believe that the findings in this present case support such an effect.

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# Treatment of scleroderma heart by D-penicillamine

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*A case of severe diffuse systemic sclerosis with cardiomegaly and cardiac failure is described. Treatment with D-penicillamine caused a pronounced decrease in heart size, together with clinical improvement. The use of penicillamine in scleroderma heart has not previously been reported.*

The use of D-penicillamine in the treatment of scleroderma (diffuse systemic sclerosis) was first reported by Fulghum and Katz (1968). Subsequently several articles have appeared reporting encouraging results, e.g. Bluestone *et al.* (1970), Tio, Van Wijk, and de Haan (1973), and Thomson and Milne (1974). In none of these papers, however, has the effect of D-penicillamine upon the scleroderma heart been reported. In the case described below cardiomegaly and mild congestive cardiac failure caused by scleroderma responded well to D-penicillamine.

## Case report

A 24-year-old West Indian nurse presented with Raynaud's disease in 1968. By 1970 this had progressed to severe fingertip ulceration, but there appeared to be no other skin involvement, the heart was not enlarged, and a barium swallow and chest *x*-ray film were normal (Fig. 1A). In 1971, sclerodactyly became pronounced and, in addition, there was skin tightening of the anterior chest wall and nasal bridge. Treatment of the Raynaud's disease was begun with griseofulvin. Dysphagia, limb muscle weakness, and obvious stiffness of the knees and elbow joints developed early in 1972, when a second barium meal showed the typical oseophagus of scleroderma, and cardiomegaly was present on *x*-ray examination for the first time (Fig. 1B). A skeletal muscle biopsy showed a fibrosis compatible with a diagnosis of diffuse systemic sclerosis.

Although treatment with prednisolone (20 mg daily) was begun (June, 1972) a decrease in exercise tolerance occurred three months later, in the absence of arrhythmias or systemic hypertension. Cardiomegaly was more pronounced on *x*-ray film, but heart sounds were normal and no failure was present. The electrocardiogram now showed left axis deviation, and widespread T wave inversion (Fig. 2A). Lung function tests showed a reduced transfer factor of 13·1 ml CO/min per mmHg (expected normal 29·3) and a reduced total lung capacity of 3·65 l (expected normal 5·83 l). Lymphocyte transformation studies in the presence of a muscle antigen showed a high positive value of 445 counts/min, compatible with an active myositis.

By March 1973 the patient's exercise tolerance had worsened further, despite treatment with prednisolone (10 mg daily), and the introduction of digoxin (0·25 mg o.d.) and diuretic therapy. On examination the patient presented as a thin woman, with severe sclerodactyly gross restriction of facial mobility, and sclerodermatous plaques on the anterior chest wall, and on the thighs. There was persistent joint pain and limitation of movement, particularly of the hips and knees. Tachycardia was absent at rest and there was no pulsus paradoxus. There was pronounced cardiomegaly and a soft mitral third sound. Blood pressure was 130/70 mm Hg (17·3/9·1 kPa).

Six months later the symptoms remained and the clinical, *x*-ray film, and electrocardiographic appearances had deteriorated (Fig. 1C and Fig. 2B). The mitral third sound was louder and in addition a soft pansystolic murmur of mitral regurgitation was audible. Antinuclear factor was positive (1/1024), lupus erythematosus cells were absent, and the serum complement $C_3$ level was 64 units/ml.

Because the patient's clinical condition was worsening despite conventional therapy, D-penicillamine treatment was begun in September 1973, with a dose of 150 mg daily. This was increased gradually over the succeeding weeks to a maintenance dose of 150 mg t.d.s. Concurrently the dose of prednisolone was reduced from 10 to 3 mg daily, but the other drugs were continued unchanged.

A slow and gradual improvement in the patient's condition ensued. After six months' treatment with

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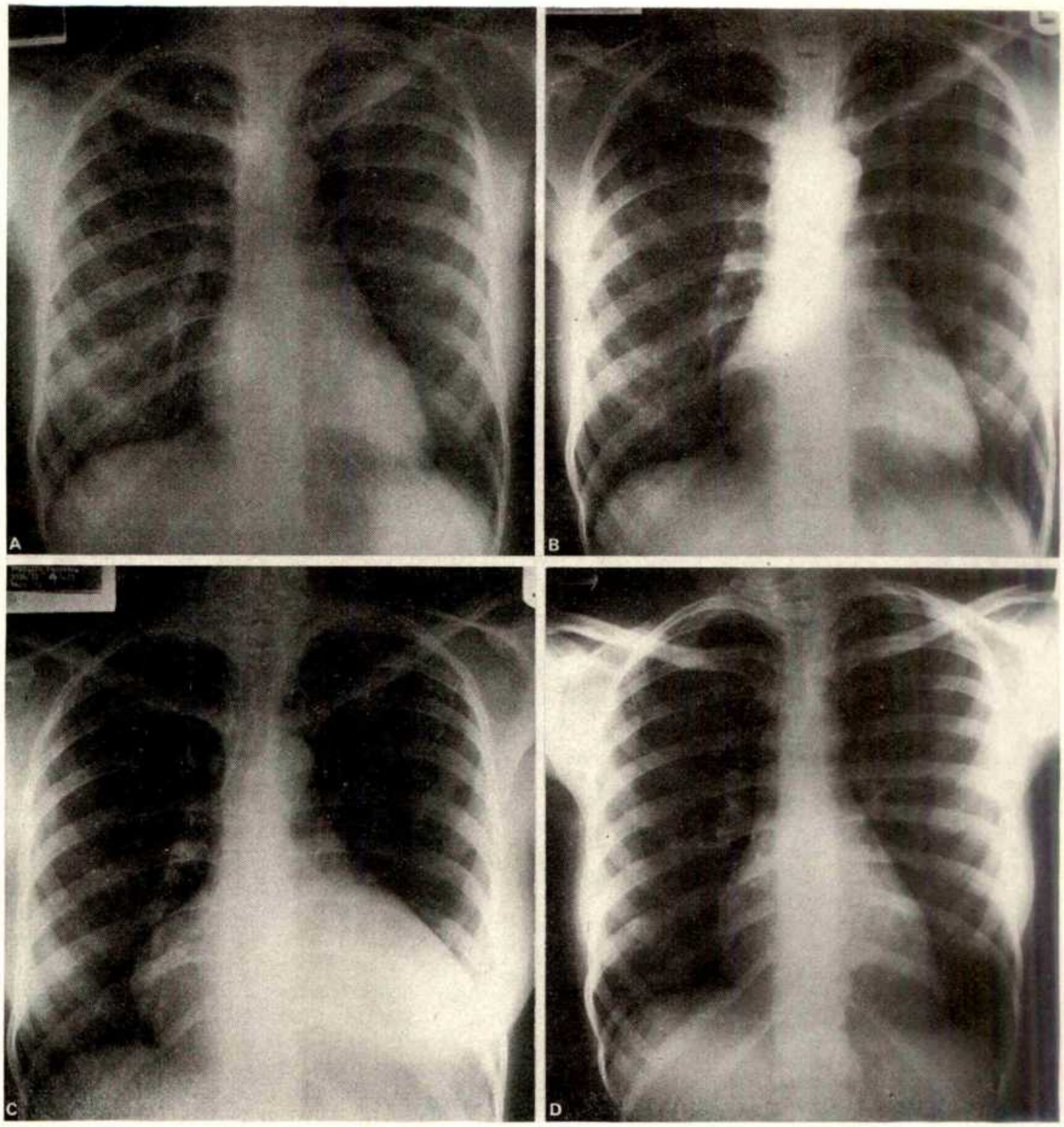

FIG. 1 *Chest x-ray films from patient with scleroderma heart. (A) before cardiac involvement (1970); (B) three months before treatment with digoxin and steroids (1972). Cardiac enlargement persisted for 15 months (C) (1973), and D-penicillamine treatment was started 2 months later. (D) Reduction in cardiomegaly after 14 months' therapy (1974).*

D-penicillamine, during which there had been no haematological or urinary abnormalities, there was a subjective increase in well-being, and an improvement in exercise tolerance to grade IIb. After a further nine months the patient was reviewed; there was an increase in facial mobility, and in joint laxity. There were now no firm plaques and no new digital ulceration. The heart was smaller (Fig. 1D) and the mitral murmur was absent and the third sound softer. There was no evidence of congestive failure and the blood pressure was unchanged. The electrocardiogram had reverted to its appearance of 1972, with reduced T wave inversion (Fig. 2C). Lung function tests at this time (November 1974) showed a slight increase in transfer factor from 13·3 to 14·3

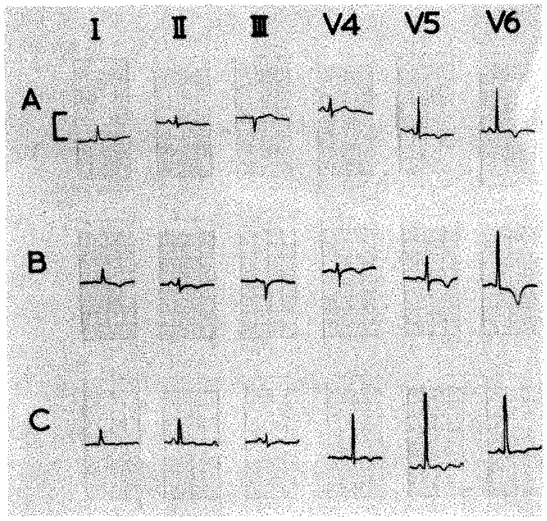

FIG. 2 *Electrocardiograms from patient with scleroderma heart. (A) After 6 months', and (B) after 14 months' treatment with steroids and digoxin but before the D-penicillamine; (C) after 15 months' treatment with D-penicillamine.*

ml CO/mm $H_2O$ per min, and an increase in total lung capacity from 3·65 l to 4·67 l. Barium swallow appearances had reverted to normal.

At the invitation of Dr. S. Oram the patient was transfered to the Cardiac Department at King's College Hospital, London, where right heart catheterization showed right ventricular pressure of 32/8 mm Hg (4·3/1·0 kPa), pulmonary artery pressure of 32/12 mm Hg (4·3/1·6 kPa), and wedge pressure (mean) 10 mm Hg (1·3 kPa). Two right ventricular endomyocardial biopsies were obtained by Dr. P. J. Richardson. Histological examination by Dr. E. G. J. Olsen showed normal muscle and vascular architecture, with no fibrosis. A repeat skeletal muscle biopsy was obtained from the left deltoid, and section here likewise showed no evidence of active muscle degeneration or myositis, but a slight increase in the fibrous interstitium.

Treatment with prednisolone (3 mg daily) and digoxin was stopped in January 1975 and in the intervening period the patient has been well. Her only symptoms recently have been of breathlessness at grade IIa exertion and occasional palpitations. The cardiac outline remains smaller on *x*-ray film. The only treatment besides D-penicillamine 125 mg b.d. is now bendrofluazide 5 mg daily with potassium supplementation, griseofulvin, and pyridoxine, the metabolism of which is disturbed by penicillamine (Gibbs and Walshe, 1966). The patient has returned to work.

## Discussion

Involvement of the heart in systemic sclerosis is rare compared with other viscera such as oesophagus or lungs, and an analysis of published data (Oram and Stokes, 1961) showed that it had been found on average in less than 15 per cent of cases. The heart is more commonly affected secondary to scleroderma of the lungs (Sackner *et al.*, 1964), but can be directly involved alone (D'Angelo *et al.*, 1969), and this may occasionally be the presenting feature of the disease. Necropsy studies have shown that the myocardium is primarily involved and that pericardial and endocardial damage is rarer. Cardiac symptoms usually occur late in the disease, and life expectancy is then short, averaging 30 months in the 21 patients personally treated by Oram and Stokes (1961). Electrocardiographic abnormalities, which may be various, are most often the first evidence of scleroderma affecting the heart, and the most common abnormality is an appearance suggesting myocardial ischaemia or infarction, as in this case. When the myocardium is involved, cardiac dilatation is the rule and grossly enlarged *x*-ray outlines have been reported in other papers.

Penicillamine (β,β dimethyl cysteine) was first introduced as a therapeutic agent by Walshe (1956, 1960) for the treatment of hepatolenticular degeneration (Wilson's disease). Its possible usefulness in the connective tissue disorders was suggested by Jaffe (1963) who showed a fall in the titre of rheumatoid factor in patients with severe rheumatoid arthritis when penicillamine was given. A careful double-blind trial (Andrews *et al.*, 1973) has shown its superiority over placebo in the treatment of severe rheumatoid arthritis, and it is now in routine use for this disease (Golding, 1973).

In 1966, Harris and Sjoerdsma suggested that penicillamine was a logical therapy for scleroderma, since it caused an increase in the 'soluble' collagen content of skin samples from patients with rheumatoid arthritis, whereas this collagen was found to be in low concentration in sclerodermatous plaques. More recently, Herbert *et al.* (1974) have shown that scleroderma skin contains an excess of the reducible cross links which occur in mature collagen between tropocollagen fibrils, and that this abnormal preponderance is reduced after treatment with penicillamine. The implication is that in active, but not in well-established lesions, penicillamine may produce an improvement as it can inhibit the formation of these links as collagen is laid down.

Clinical experience with penicillamine in systemic sclerosis has been varied and sporadic and to date no comparative trials have been published. Bluestone *et al.* (1970) reported that 6 of 9 treated patients with systemic disease showed an objective improvement in skin elasticity, and Moynahan (1973) has shown a consistent clinical improvement in childhood morphoea treated with this drug. A 12-year-old girl with multisystem disease treated with penicillamine for two years showed, similarly, improvement in cutaneous, oesophageal, and Raynaud symptoms, but had no change in lung function, erythrocyte sedimentation rate, or antinuclear factor titre (Thomson and Milne, 1974),

The association of a cardiac lesion with scleroderma does not necessarily establish the presence of scleroderma in the heart. However, the undoubted clinical syndrome of diffuse disease in our patient, coupled with the absence of any other explanation for the pronounced cardiomegaly, electrocardiographic abnormalities, and cardiac failure, seem to justify the diagnosis. A negative right ventricular endomyocardial biopsy after 15 months' treatment does not necessarily deny it, since the sclerodermatous process is patchily distributed within the myocardium, and the endocardium frequently escapes (D'Angelo *et al.*, 1969). At the start of the penicillamine therapy, with multisystem disease affecting both heart and lungs, this patient's condi tion would not have been expected to improve. A series of *x*-ray films in the absence of any clinical evidence of pericardial effusion indicated that the cardiomegaly had persistently worsened for 10 months, despite steroid therapy. After penicillamine treatment was begun, however, the heart size steadily decreased and this change was accompanied *pari passu* by an improvement in the electrocardiogram, an increase in skin and joint suppleness, and loss of muscle stiffness. This decrease in cardiomegaly cannot be ascribed to the continued low dose of steroids, since this is not known to cause cardiac resolution in much larger doses, and the small dose was continued in this patient primarily as supportive treatment for the joint pain, as was the griseofulvin for the Raynaud's disease. We cannot exclude the possibility from a single case history that a spontaneous remission in the disease has taken place. However, a spontaneous remission in advanced disease so rapid and complete would be unexpected, and we conclude that the use of penicillamine contributed to the improvement in this patient's scleroderma heart.

We are indebted to Dr. Margaret Walshe for advice on the dermatological aspects of this case, to Dr. Samuel Oram, Dr. P. J. Richardson, and Dr. E. G. J. Olsen for arranging the endomyocardial biopsy, and Dr. Elizabeth Hills for doing the lung function tests.

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# Mobitz II AV block within the His bundle, with progression to complete heart block

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*A case of a 48-year-old woman with frequent syncopal episodes is reported. The electrocardiogram showed high degree AV block with narrow QRS complexes. The His bundle electrogram displayed a split His deflection indicating impairment of conduction within the His bundle of the Mobitz II type. The AH interval was prolonged and Wenckebach phenomenon occurred at the same atrial pacing rate before and after atropine administration. During spontaneous or induced high grade AV block an escape rhythm originating in the distal His bundle was observed.*

*A second study performed one year later showed progression to complete AV block. Both His potentials were present, one following the atrial and the other preceding the ventricular deflection. The H'V interval was prolonged and a further lengthening was seen after ajmaline. All these findings indicated proximal, mid, and distal disease of the His trunk.*

Different degrees of atrioventricular conduction disturbances may occur within the His bundle (Narula, Scherlag, and Samet, 1969; Narula and Samet, 1970). High grade second degree AV block and complete AV block caused by lesions in the His bundle may be suspected in the electrocardiogram if the QRS complexes are narrow (Narula and Samet, 1970). These diagnoses may be confirmed if split His deflections are recorded in the His bundle electrogram (Schuilenburg and Durrer, 1972; Gupta, Lichstein, and Chadda, 1972). The purpose of this communication is to report a case of high degree Mobitz II AV block which progressed to complete heart block within one year. Initially, the His bundle electrogram showed split His potentials and when complete heart block developed the subsidiary pacemaker was located in the distal His bundle.

## Case report

The patient was a 48-year-old woman with frequent syncopal episodes. There was no history of chest pain or high blood pressure. Serological investigations for Chagas' disease were negative. The electrocardiogram showed Mobitz II type second degree AV block, with a PR interval of 0·26 s in the conducted beats and QRS complexes of 0·10 s duration displaying a right bundle-branch conduction disturbance pattern. Following two or more blocked sinus P waves, escape junctional beats occurred with a slightly different QRS morphology and similar duration. Blocked supraventricular extrasystoles were also present.

A His bundle electrogram was obtained with the standard technique (Scherlag *et al.*, 1969). Another bipolar electrode catheter was placed in the high right atrium to record an atrial electrogram. The same catheter was used for atrial pacing. All tracings were recorded at a speed of 100 mm/s. A direct writing eight-channel Elema recorder was employed.

The initial tracing showed 1:1 AV conduction. Two His bundle spikes were recorded in the AV interval. The AH interval measured 125 ms, the HH' interval 95 ms, and the H'V interval 30 ms. The QRS morphology in V1 showed an incomplete right bundle-branch block pattern. Fig. 1 is a continuous recording showing spontaneous changes in AV conduction. The first 5 beats are similar to those seen in the initial tracing and have an almost constant HH' interval varying between 85 and 92 ms. The sixth atrial beat of the atrial electrogram was premature and occurs simultaneously with the fifth QRS complex initiating a period of three blocked A waves followed by H at the same previous interval. The AV conduction was then interrupted and an escape rhythm lasting for 6 beats was

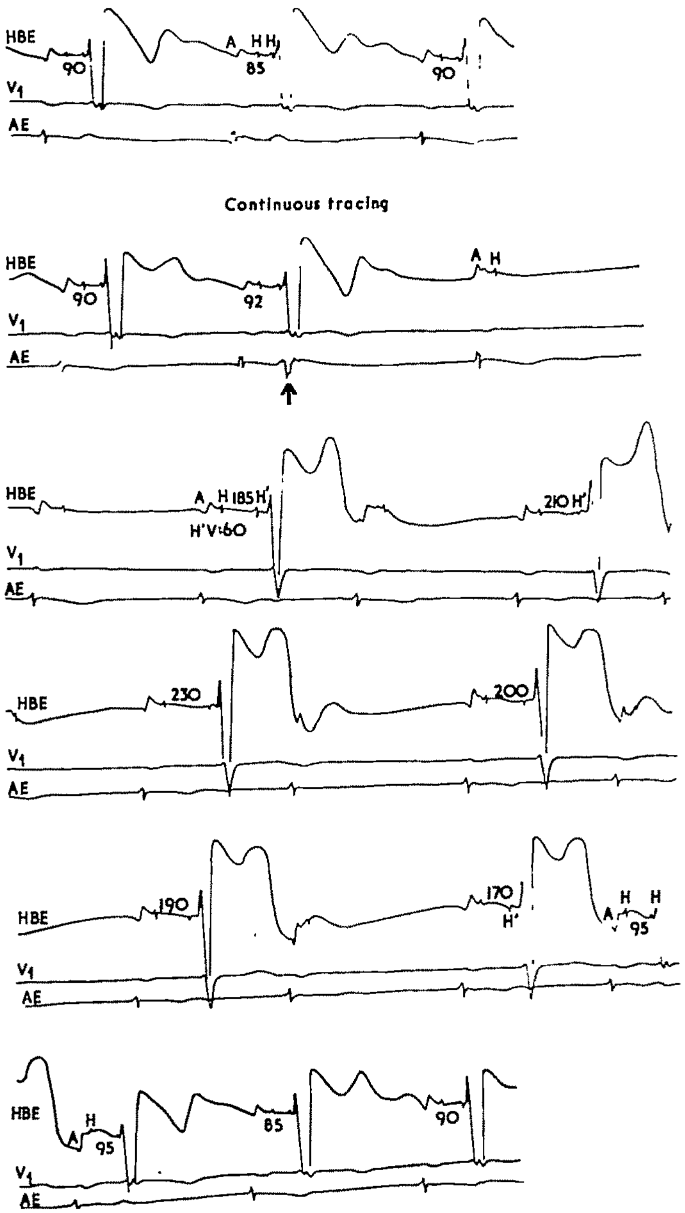

FIG. 1 *Continuous tracing. From top to bottom, His bundle electrogram (HBE), lead V1, and atrial electrogram (AE), are displayed. The numbers indicate the length of the HH' intervals in ms. The sixth atrial complex (arrow) is premature and occurs simultaneously with the fifth QRS complex. For further explanation see text.*

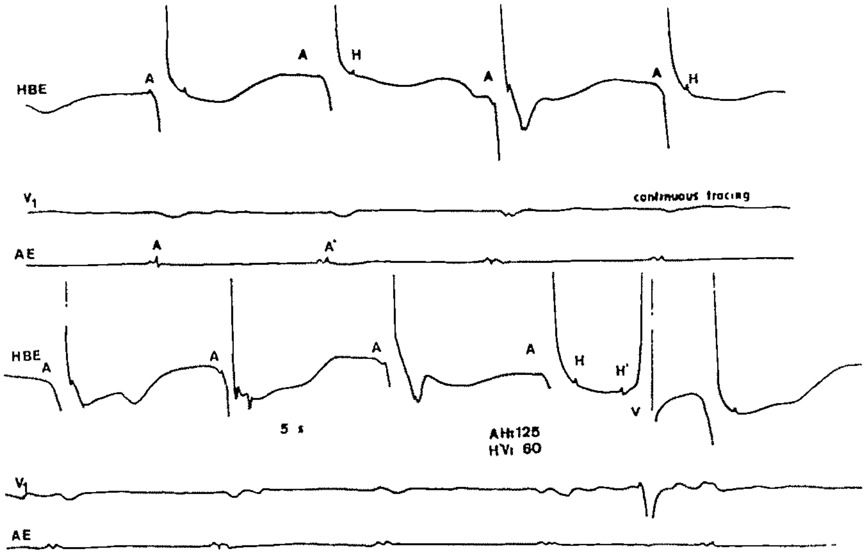

FIG. 2 *Continuous tracing showing a long period of AV block. Every A wave is followed by an H deflection at the same interval. Following the eighth A wave an escape beat appears. Abbreviations as in previous figure.*

observed. The escape beats during this period were preceded by an H′ deflection with an H′V interval of 60 ms which was much longer than that observed in conducted beats. The QRS configuration in V1 during this rhythm did not show the IRBBB pattern. Every second atrial complex was followed by an H′ spike, but the changing HH′ interval indicated that there were two independent rhythms. One-to-one AV conduction resumed after the sixth escape beat. Fig. 2 shows a more severe depression of the AV conduction lasting 5 s also occurring spontaneously. Every A deflection was followed by H at the same interval and the escape beat had the same characteristics as those of the previous figure.

Atrial pacing at a rate of 100/min induced 2:1 AV block. Every A deflection was followed by H when nonconducted. In the conducted beats the two H deflections appeared as in the basal tracing. The AH interval was prolonged to 180 ms in both blocked and conducted beats. The H′V interval and the QRS morphology in V1 were unchanged. Also noted were the occurrence of higher degrees of AV block with escape beats similar to those already described. An increase in the atrial pacing rate to 120/min induced Wenckebach phenomenon in the AH interval. Atropine administration also induced 2:1 intra-His AV block but did not change the basal AH (130 ms), HH′ (95 ms), or H′V (30 ms) intervals. Atrial overdriving after atropine again elicited a Wenckebach phenomenon in the AH interval at an atrial pacing rate of 120/min.

A permanent transvenous demand pacemaker was inserted and she did well for about a year when once again she started to notice dizziness; intermittent pacemaker failure was diagnosed. The pacemaker malfunction was the result of increased endocardial threshold. A new unit with epicardial electrodes was implanted. A His bundle electrogram was repeated at the time of replacement. The second study showed complete AV block with an atrial rate of 90 per minute. Every A wave was followed by H at an interval of 140 ms. The ventricular rate was 43 per minute. All ventricular complexes were similar in morphology to those seen in the escape beats of the first study and were preceded by an H′ deflection with an H′V interval of 60 ms (Fig. 3). Ajmaline, 50 mg, was given intravenously inducing prolongation of the H′V interval to 75 ms (Fig. 3). The AH interval and the ventricular rate did not change.

## Comment

The His bundle electrogram unmasked the site and mechanism of block in this patient. The presence of split His potentials separated by a 95 ms interval indicated a conduction disturbance within the His bundle. The first H deflection was a proximal His potential as supported by the prolongation of the AH interval during pacing. The origin of the H′ deflection in the conducted beats was probably

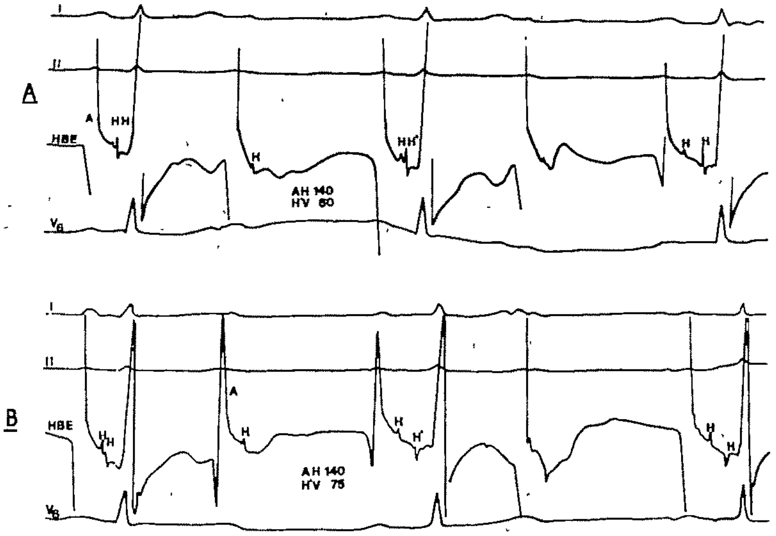

FIG. 3 *(A) Basal tracing of the second study showing complete AV block. The ventricular complexes are preceded by H' deflections and every atrial complex is followed by H at the same interval. (B) Tracing displaying the effect of 50 mg ajmaline given intravenously. The H'V interval has been prolonged from 60 to 75 ms. The AH interval remains unchanged. The His bundle electrogram (HBE) has been recorded simultaneously with leads I, II, and V6.*

in the right bundle-branch since the H'V interval was only 30 ms. The HH' interval of all conducted beats remained constant indicating that the type of block present in this patient was Mobitz II within the His bundle.

During episodes of higher degrees of heart block, either occurring spontaneously or induced by atrial pacing, escape beats from the distal part of the His bundle appeared. These escapes were initiated by an H' deflection with an H'V interval of 60 ms. The lack of relation between H and H' signals indicated the existence of independent rhythms. The longer H'V interval in the escape beats as opposed to the conducted beats suggested that the subsidiary pacemaker was located in the distal His bundle. It was also noticed that the QRS morphology showing an incomplete right bundle-branch block pattern in the conducted beats changed to a more normal configuration during the escape rhythm even though the QRS width did not change significantly. The apparent improvement of intraventricular conduction could be explained on the basis that the right bundle-branch disturbance was rate dependent (García and Rosenbaum, 1972).

Right atrial pacing and atropine administration induced higher degrees of AV block with the expected opposite effects on the AH interval. However, this interval remained longer than normal (130 ms) even after atropine. A prolonged AH interval could be either the result of a conduction delay in the AV node or in the proximal His bundle. Since atropine does not improve conduction through the His bundle as shown by Akhtar *et al.* (1974), it is most likely that the delay occurred in the infra-AV nodal origin of the His trunk. This was further supported by the fact that Wenckebach phenomenon in the AH interval occurred at the same atrial pacing rate both before and after atropine administration.

The follow-up study obtained after a year at the time of pacemaker replacement disclosed complete heart block within the His bundle. Every A deflection was followed by H and the ventricular deflection was preceded by H'. The H'V interval and the QRS configuration were similar to those seen in the first study during the escape rhythm. The lengthening of the H'V interval observed with ajmaline administration with no change in the atrial or ventricular rates supported the origin of H' in the distal His bundle (Camerini *et al.*, 1973).

This patient displayed several interesting features. When she was first studied there was Mobitz II AV block within the His bundle with narrow QRS complexes. During spontaneous or induced higher degrees of AV block the subsidiary pacemaker was located in the distal His bundle. At the time of the second study the block had progressed to third degree with the same subsidiary pacemaker. On both occasions the two potentials originated in the His bundle were recorded without any difficulty. It has recently been mentioned that in certain cases the recording of split His signals might be technically difficult (Schuilenburg and Durrer, 1975).

The prolonged AH interval with the occurrence of Wenckebach phenomenon at similar atrial pacing rates before and after atropine, the split His signal with progression to complete AV block, and the long H'V interval which lengthened further with ajmaline, indicated proximal, mid, and distal disease of the His trunk ('pan His disease').

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# British Cardiac Society

The 55th Annual General Meeting was held in Edinburgh on 31 March and 1 April.

The Annual Dinner was held at the Royal College of Physicians of Edinburgh and R. M. Marquis was in the Chair.

At the Private Business Meeting the retiring President, J. F. Goodwin, introduced the newly-elected Officers and Council member. They are: President, W. Somerville; Honorary Secretary, G. A. H. Miller; Treasurer, D. Krikler; Honorary Assistant Secretary, B. L. Pentecost; Council Member, Celia Oakley.

At the Scientific Meeting, with R. M. Marquis in the Chair, the following short communications were given.

## Natural history of postinfarction angina pectoris

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Four hundred and seventy-one male survivors of a first myocardial infarction under 60 years were followed for a period of two years. All were subjected to a long-term exercise and secondary prevention programme. An early return to work was encouraged. One hundred and seventy-three (36·7%) suffered from postinfarction angina pectoris of whom 50 had preinfarction angina of at least three months' duration. The two-year mortality was similar for the angina and non-angina groups but the recurrence of non-fatal attacks was higher in the anginal group. The difference was just short of the 5 per cent level of significance. Nearly 40 per cent of patients with angina showed improvement or resolution of their symptoms at the end of the period of follow-up. Forty-three per cent remained unchanged. Only six patients showed sustained disimprovement. Ninety-four per cent of the non-anginal group and 89·7 per cent of the anginal group had returned to work by the end of the period of follow-up. Only four patients suffered from disabling angina. No anginal patient was subjected to bypass surgery and 70 per cent received no specific antianginal treatment such as beta-blockers or glyceryl trinitrate.

## Controlled trial of fibrinolytic therapy in unstable angina

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Unstable angina is frequently a premonitory symptom of myocardial infarction. We report the results of a single blind controlled trial designed to assess the influence of fibrinolytic therapy in this setting.

The diagnosis of unstable angina was based on W.H.O. guidelines. Unequivocal electrocardiographic evidence of ischaemia was mandatory. Patients were excluded before randomization by any contraindication to fibrinolytic therapy or if angina stabilized during a short observation period.

Over two years 40 patients were accepted to the trial. They were randomly allocated to treatment with streptokinase for 24 hours followed by warfarin or to warfarin therapy alone. Treatment of both groups was otherwise similar.

Of 20 patients treated with streptokinase only 1 suffered a cardiovascular event—sudden (presumably arrhythmic) death 8 days after treatment. Of 20 patients treated with warfarin alone, 3 died suddenly and a further 5 developed myocardial infarction.

The excess of cardiovascular events (myocardial infarction and sudden death) in the warfarin treated group is significant. ($P < 0·02$.)

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## Possible explanation for protective action of long-term beta-adrenoceptor blockade after myocardial infarction

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Beta-adrenoceptor antagonists are clinically effective antianginal and antidysrhythmic agents and have recently been shown to improve the prognosis of myocardial infarction, but their mode of action has not been wholly explained. While experimental investigation has concentrated on elucidating the acute effects of beta-blockade, full therapeutic benefit in patients is not seen for several weeks. The electrophysiological effects of prolonged administration of three different beta-adrenoceptor antagonists were, therefore, studied.

Rabbits were dosed with propranolol, practolol, acebutolol or saline. Electrocardiograms were recorded throughout the treatment period. These showed that in all treated animals rate-corrected QT interval (QTc) began to lengthen after 5 days' dosing, and by day 15 reached a constant prolongation (+11·0%, SEM 1·1, P< <0·001). Subsequent microelectrode studies on atria and ventricles of the hearts removed after 6 weeks' treatment showed significant prolongation of action potential duration in all treated animals which paralleled the *in vivo* QTc lengthening.

It is concluded that prolonged beta-adrenoceptor blockade induces a long-term adaptation in cardiac function quite distinct from the acute effects of beta-blockade. Since an increase in action potential duration is known to be antidysrhythmic, this could account for the protective action of long-term beta-blockade after myocardial infarction.

### Surgical treatment of aneurysms of ascending aorta

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Among 75 patients treated surgically for ascending aortic aneurysms during a 5-year period, there was haemodynamically significant aortic regurgitation in 67. The valve was replaced in 56 patients, using either a fresh aortic homograft (51) or a Starr-Edwards prosthesis (5). In 11 cases it was possible to conserve the patient's own valve by repair and resuspension of the cusps. Coronary artery involvement necessitated reimplantation in 7 while in 4 dissection extending into the proximal coronary was bypassed with vein grafts. Twenty-seven patients were operated as emergencies for acute dissection or rupture with an early mortality of 15 per cent, while operative mortality was 4 per cent for elective procedures. There were 2 late deaths, and 1 patient with the Marfan's syndrome required a second operation for recurrent aortic regurgitation after valve repair. Histological examination of the aortas disclosed a wide range of underlying pathology. Medionecrosis in 44, aortitis in 19, arteriosclerosis in 6, and infection in 6. Follow-up of patients for periods of 6 months to 5 years has shown maintenance of the good initial haemodynamic results.

### Non-invasive assessment of left ventricular function before and after aortic valve replacement for severe aortic reflux

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and D. J. Brown
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In 20 patients who underwent aortic valve replacement for severe aortic reflux, simultaneous apex cardiograms and left ventricular endocardial echocardiograms were recorded before operation, and repeated in the 4 weeks after surgery. The left ventricular echoes and apex cardiograms were digitized so that instantaneous left ventricular dimension, rate of change, and velocity of circumferential fibre shortening could be derived, and a loop describing the time relation between change in left ventricular dimension and apex cardiogram plotted. Incoordinate contraction and relaxation were recognizable by changes in shape of this loop. These parameters were used to study the effects of surgery on left ventricular function.

After aortic valve replacement, there was an early reduction in end-diastolic dimension from 7·0±0·8 cm to 5·7±1·0 cm (P<0·001) and no significant change in end-systolic dimension, while peak $V^{cf}$ fell from 1·9±0·6 to 1·4±0·4 s$^{-1}$ (P<0·01), and was unchanged subsequently. In the early postoperative period there were distinct abnormalities of isovolumic contraction and to a less extent of isovolumic relaxation which resolved in the first week except in 2 patients who developed protracted low output states.

After aortic valve replacement there is an early reduction in diastolic dimension, deterioration in peak $V^{cf}$, and a variable period of incoordinate contraction and relaxation.

### Early closure of ventricular septal defect complicating myocardial infarction

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In an 18-month period 6 patients were submitted to operation for ventricular septal rupture which had occurred within one week of acute myocardial infarction. All had sudden occurrence of a harsh systolic murmur and rapidly developed gross cardiac failure. Two were in cardiogenic shock by the time of operation. Complete preoperative investigation included right and left heart catheterization with biplane left ventricular cineangiography and coronary arteriography.

Four patients required operation 8 to 25 days after infarction and the other 2 were operated on after 4 and 7 months. The principal of 'total correction' of all cardiac pathology was applied so that in addition to closure of the septal defect, each patient had additional operative procedures—resection of left ventricular infarct or aneurysm (all patients), mitral valve replacement (1 patient) or coronary artery vein bypass grafts (5 patients). All 6 patients survived operation, with immediate improvement in their haemodynamic state so that none required mechanical assistance postoperatively. One patient died 4 weeks postoperatively from perforation of an acute peptic ulcer and 1 required reclosure of the defect which recurred on the second postoperative day. The 5 surviving patients remain very well at follow-up.

It is recommended that such patients should have early complete investigation and immediate surgical correction when medical treatment proves inadequate.

## Comparison of measurement of ejection fraction by radioisotope techniques and by cineangiography

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Until recently the measurement of ejection fraction has relied on data from cardiac catheterization, but radioisotope techniques offer a promising, non-invasive alternative.

We have measured the ejection fraction in 20 patients with ischaemic heart disease using two different radioisotope techniques, either by following the rapid fluctuations in count-rate after the injection of a bolus of 10 mCi of Technetium$^{99}$m in its passage through the left ventricle, or by using our own modification of an accumulative method proposed by Zaret and colleagues (1971). Our own technique uses a simple gated electronic circuit which allows analysis of the change in ventricular volume throughout the cardiac cycle and makes no assumptions with regard to ventricular geometry. We have compared the ejection fraction measured by these radioisotope methods with the ejection fraction measured by cineangiography.

We have obtained a good correlation between these two isotope methods ($r=0{\cdot}91$) and between ejection fraction measured by these methods and by cineangiography ($r=0{\cdot}87$). The gated isotope technique which allows measurement of very low ejection fractions and also allows analysis of the rate of volume change, offers a valuable non-invasive means of investigating left ventricular function.

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## Initial clinical experience with stented porcine aortic valve xenograft

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In recent years the gluteraldehyde preserved porcine xenograft mounted on a flexible stent (Hancock Laboratories) has been increasingly used for human heart valve replacement. These valves were first used in Edinburgh in November 1973, and our 2-year experience with them is presented.

Seventy-six Hancock valves were inserted in 66 patients, 33 male and 33 female. Their average age was 55 years (range 14-68 years). The indication for operation was rheumatic heart disease (38 patients), papillary muscle dysfunction (8 patients), prosthetic valve dysfunction (8 patients), congenital abnormality (4 patients), degenerative valve disease (4 patients), SBE (3 patients), and luetic disease (1 patient).

Forty-six valves were placed in the mitral, 28 in the aortic, and 2 in the tricuspid position; 10 patients required double valve replacement. Additional operative procedures included coronary artery vein bypass grafts (12 patients), tricuspid annuloplasty (6 patients), open mitral valvotomy (3 patients), left ventricular aneurysmectomy (2 patients), and replacement of the ascending aorta (1 patient). There were 2 hospital deaths (3%).

Oral anticoagulation was continued for approximately 6 weeks postoperatively when it was discontinued in all but 8 patients.

In the follow-up period (3 to 26 months) there were 3 late deaths, 2 of which were sudden. There was no documented episode of thromboembolism or valve degeneration. All except 2 patients were clinically improved from N.Y.H.A. class III or IV preoperatively to class I or II postoperatively.

Initial results with Hancock valves are satisfactory but further follow-up is required to determine their long-term durability.

## Pregnancy after valve replacement

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A questionnaire sent to cardiologists in the U.K. yielded details of 25 pregnancies in 22 patients to which were added 5 personal cases.

Eighteen pregnancies in 15 women who were not given anticoagulants produced 17 healthy babies and 1 spontaneous abortion. This group included 8 patients with tissue mitral valve replacements, 5 of whom were in atrial fibrillation, as well as 6 who had free aortic homografts. There were no maternal complications.

Thirteen pregnancies in 12 women who received anticoagulants gave rise to 5 healthy babies. This group included 11 patients with mitral valve prostheses, 9 of whom were in atrial fibrillation. There were no thromboembolic complications in patients taking oral anticoagulants.

In 3 additional patients the valve replacement was carried out during pregnancy.

Most women with valve replacements tolerate the haemodynamic load of pregnancy easily and without personal hazard. A high fetal wastage in women taking oral anticoagulants with transfer to heparin before term is largely attributable to haemorrhage *in utero* but partly to malformation. The withholding of anticoagulants would usually be undesirable in patients with prosthetic valves but warfarin should be avoided in pregnancy because of teratogenicity.

The advantages of biological valves in young women were apparent in this series.

## Myocardial lacate metabolism and coronary venous phosphate in cyanotic congenital heart disease

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To define the myocardial metabolic adaptation to cyanotic heart disease, coronary arteriovenous metabolic differences were measured at rest and after atrial pacing. During atrial pacing (150–180 min) for 5–10 min, lactate extraction in 7 non-cyanotic controls decreased from 27 ±5 to 16 ±4 per cent ($P < 0.05$). Cyanotic patients fell into 2 groups: 9 patients (group I) showed a drop in arterial $O_2$ saturation ($SaO_2$) with atrial pacing, from 76 ±3 per cent to 55 ±5 per cent; their lactate extraction fell sharply from 29 ±2 to 3 ±6 per cent ($P < 0.001$). Five cyanotic patients (group II showed no fall in $SaO_2$ with atrial pacing, and lactate extraction remained stable (27 ±2%). Inorganic phosphate extraction was noted in all patients at rest; this disappeared with atrial pacing in controls and cyanotic group I, but not in group II. No potassium changes were seen in any patients. The combination of the release of lactate and phosphate during pacing in group I cyanotics showed breakdown of high energy phosphate compounds and activation of anaerobic glycolysis in the myocardium. The absence of such changes in group II cyanotic patients indicates adaptation which allows the stress of pacing to be withstood more satisfactorily than in controls.

## Assessment of subendocardial ischaemia during open heart surgery using intramyocardial oxygen and electrocardiographic electrodes

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Recent animal studies have shown that the low cardiac output syndromes seen in the post-cardiopulmonary bypass period may be secondary to ischaemic haemorrhagic necrosis of the subendocardial portion of the left ventricle.

The occurrence of subendocardial ischaemia in patients during cardiopulmonary bypass was assessed on a minute-to-minute basis using ST segment elevations in unipolar intramyocardial electrograms and intramyocardial oxygen tensions measured in the subendocardium and subepicardium. Fifteen point platinum plunge electrodes were constructed in 22-gauge stainless steel needles and placed in the anterior right and left ventricular walls in patients during surgery. Changes in ST elevation and myocardial oxygen tension were correlated with ischaemic and reperfusion times on cardiopulmonary bypass. In no patient was elevated ST segment seen before bypass or during perfusion before aortic cross-clamping. Simultaneous intramyocardial oxygen tension during these periods was $PO_2=19{\cdot}1\pm3{\cdot}1$. Four patients developed a very depressed mechanical function in the postoperative period and also showed a distinct increase in preferential subendocardial extracellular ST elevation. Seven patients had a significant increase in the subendocardial ST elevation at the termination of bypass when the beating non-working heart was separated from bypass and converted to a beating, working heart, and 3 of these patients required isoprenaline support. Elevations of ST segment were noted only in the subendocardium in these patients, showing that intraoperative intramyocardial $PO_2$ and electrograms allowed a minute-to-minute evaluation of regional oxygen supply/demand ratio in patients undergoing cardiopulmonary bypass.

## Emergency treatment of certain cyanotic heart defects with prostaglandin $E_2$

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Newborn infants with pulmonary atresia are almost entirely dependent on continued patency of the ductus arteriosus for their pulmonary blood flow. When the ductus constricts they develop severe hypoxia, metabolic acidosis, and without intervention usually die. Our demonstration that E type prostaglandins conspicuously relax the ductus smooth muscle in fetal lambs suggested a new approach to the emergency management of patients with pulmonary atresia and similar lesions. During diagnostic catheterization we have infused Prostin $E_2$ (Prostaglandin $E_2$ Upjohn) 0·1 mg/kg per min into 5 neonates with various cyanotic cardiac malformations and ductus dependent pulmonary blood flow. Two further hypoxic patients, one with transposition and a failed balloon septostomy and the other with critical pulmonary stenosis in whom surgery had been unsuccessful, were also treated with a similar infusion. $PaO_2$ was measured before and after a 10-min test infusion and rose significantly in every patient. The mean increase in $PaO_2$ was 14 mmHg (1·9 kPa) and in arterial oxygen saturation the mean rise was 25 per cent. Apart from a slight fall in systemic blood pressure no untoward effects were observed during the test infusion. Based on this favourable reponse the infusion was continued in these 7 patients until emergency surgery a maximum of 15 hours later. At operation the ductus was found to be widely patent in 6 of the 7, no problems were encountered with bleeding, and 6 of the 7 patients survived surgery and have done well to date. Initial experience with this new approach to the immediate management of this type of malformation is encouraging.

## Pulmonary atresia: assessment by lung imaging of pulmonary perfusion before and after operation

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The surgical management of complex pulmonary atresia poses difficulties because of the presence of large systemic collaterals and small underdeveloped pulmonary arteries. In order to investigate the changing pulmonary blood flow after staged and radical surgical procedures, conventional lung imaging with $^{99m}Tc$ labelled albumin microspheres was used in 23 patients.

Using the visual display processor of the Elscint dual-headed scanner, venous admixture shunt was measured as the difference between the summed lung activity and the total torso activity and expressed as a percentage of the total. The change in pulmonary perfusion distribution was scored for each lung using the quantitative colour display.

In patients having Blalock operations, improved lung perfusion scores on the side of the operation occurred with little alteration of the venous admixture shunt. Those undergoing radical correction where collaterals were also ligated showed distinct perfusion changes to each lung, while the venous admixture shunt fell on average from 23 per cent to 8 per cent—probably normal for the microsphere technique in this context.

This pilot study showed that routine lung imaging before and after operation for complex pulmonary atresia provides an early non-invasive means of assessment of its effect on pulmonary perfusion.

## Echocardiographic diagnosis of corrected transposition

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Corrected transposition can best be defined as transposition with atrioventricular discordance. It is often difficult to diagnose, even with angiography, since the diagnosis depends upon accurate identification of ventricular chambers. Studies on the conducting tissue in corrected transposition have shown that precise diagnosis is essential for safe surgical repair of associated anomalies. The anatomical arrangement of the heart suggests that echocardiography could play a vital role in precise diagnosis. Thus in the situs solitus individual the right-sided anterior (morphologically mitral) valve is in fibrous continuity with the pulmonary valve. The left-sided posterior (morphologically tricuspid) valve is discontinuous from the aortic valve which is usually anterior and left sided. The interventricular septum is in the anteroposterior position.

Echocardiography performed in 7 patients with corrected transposition confirmed these features. The anterior atrioventricular valve exhibited excursion of both anterior and posterior cusps, features typical of a mitral valve. It was 'continuous' with the posterior semilunar valve. The interventricular septum was sagittally orientated. The posterior atrioventricular valve was frequently dysplastic and was discontinuous from the anterior semilunar valve. The only other condition that could give this anatomical arrangement is the exceedingly rare anatomically corrected malposition with absorption of the subaortic conus.

## Transposition of great arteries, ventricular septal defect, and left ventricular outflow tract obstruction: results of 23 Rastelli operations

W. Daenen, M. de Leval, and J. Stark
Hospital for Sick Children, Great Ormond Street, London

Twenty-three patients with transposition of the great arteries (TGA), ventricular septal defect (VSD), and left ventricular outflow tract obstruction (LVOTO) had Rastelli operations between July 1971 and December 1975. Age at operation ranged between 2 and 14 years. Associated lesions included: atrial septal defect (10), patient foramen ovale (7), left superior vena cava (4), abnormal attachment of tricuspid and mitral valve (3), other (3). Previous operations included: Blalock-Taussig shunt (19), Waterston shunt (1), Blalock-Hanlon procedure (6), banding of the pulmonary artery (2), and Mustard operation (1).

Rastelli operations were performed on cardiopulmonary bypass with moderate hypothermia and intermittent cross-clamping of the aorta. The left ventricle was connected to the aorta through the VSD, which was enlarged in 15 patients. Continuity between the right ventricle and the pulmonary artery was established with a 'dacron' conduit containing an aortic homograft (10) or a porcine heterograft (13). There were 2 hospital deaths (8%). The first patient died in low cardiac output, the second died during reoperation for severe tricuspid incompetence and residual VSD. Two patients (8) died suddenly after 5 and 13 months, respectively. The cause of death was not explained at necropsy in the latter one.

## Anatomical correction of transposition of great arteries and ventricular septal defect

M. Yacoub and R. Radley-Smith
Harefield Hospital, Middlesex

Mustard's operation of inflow correction has been accepted as the method of choice for treating patients with transposition of the great arteries (TGA); this however does not constitute total correction. The ideal operation for TGA should consist of transecting the aorta and pulmonary arteries and reattaching them to the appropriate ventricles; this should include the origin of the coronary arteries. Two patients with TGA and ventricular septal defect (VSD) were treated by this method. The VSD was closed through a transverse ventriculotomy using a 'dacron' patch. The ages at the time of operation were 8 weeks and 5 years. The younger child was operated on as an emergency because of cyanosis and severe heart failure resistant to intensive medical therapy. The older child had had previous banding of the pulmonary artery at the age of 1 year. In both patients pulmonary artery pressure dropped to below half systemic immediately after the operation. Postoperative progress has been satisfactory with relief of cyanosis and heart failure.

It is concluded that early anatomical correction of TGA and VSD should play an important role in the management of these patients.

### Correction of total anomalous pulmonary venous drainage in infancy

D. Clarke, M. de Leval, J. Pincott, and J. Stark
The Thoracic Unit, Hospital for Sick Children, Great Ormond Street, London WC1

Between May 1971 and December 1975, 39 infants underwent correction of total anomalous pulmonary venous drainage (TAPVD) in this Unit. Fourteen of the 39 patients were under 1 month of age at the time of operation. Twenty-four out of 39 had supracardiac type, 7 had intracardiac type, 6 had infracardiac type, and 2 had mixed type TAPVD. The overall hospital mortality was 36 per cent compared with 68 per cent for 47 patients operated between 1963 and 1970. There were no late deaths. The improvement in survival rate in this series was attributed to: (a) earlier recognition and prompt referral, (b) an aggressive approach to diagnosis involving complete cardiac catheterization and angiocardiography to show the exact site of drainage of all pulmonary veins and to exclude any additional cardiac lesions, (c) vigorous preoperative care, (d) early complete correction, including construction of a large anastomosis and enlargement of the left atrium when indicated, (e) intensive postoperative management, paying particular attention to fluid balance, acid base status, and treatment of pulmonary complications. Mortality related to age, type of lesion, and presence of pulmonary hypertension or pulmonary venous obstruction is discussed.

### Evaluation of early primary repair of ventricular septal defect in first year of life

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Harefield Hospital, Middlesex

It has been our policy to perform primary repair of ventricular septal defect in all patients requiring operation. Indications for operation have been severe intractable cardiac failure or persistent pulmonary hypertension to systemic level in infants approaching the age of 1 year in an attempt to prevent premanent pulmonary vascular disease. Fifteen infants between the age of 1 month and 1 year underwent operation. Their weights were between 2·1 and 11 kg. All patients preoperatively had pulmonary artery pressures at or within 10 mmHg (1·3 kPa) of systemic level. All patients had the defect patched with 'dacron' through a transverse ventriculotomy. There was an immediate fall in pulmonary artery pressure to less than half systemic pressure in all patients. There was 1 early death and no late deaths. The remaining patients are asymptomatic and not requiring antifailure treatment. Late cardiac catheterization was performed 1 to 3 years after operation in 8 patients and showed normal pulmonary artery pressures and normal response to exercise. It is concluded that early repair of ventricular septal defect gives satisfactory results and appears to prevent pulmonary vascular disease.

### Anatomy of ventricular pre-excitation

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Wilhelmina Gasthuis, Amsterdam, and Brompton Hospital, London

Ventricular pre-excitation results from short-circuiting of the normal atrioventricular delay induced by the atrioventricular node. Theoretically this bypass can result through accessory atrioventricular, node-ventricular, fasciculo-ventricular, or atrio-fascicular connexions, or through intranodal bypass tracts. We examined 53 normal hearts and 8 hearts with ventricular pre-excitation of Wolff-Parkinson-White variety. The morphology of the atrioventricular fibrous anuli and their relation to the conducting tissues and pre-excitation were examined. In the normal hearts the fibrous anuli were not of uniform morphology. In places the atrial and ventricular myocardium on the right side was separated only by sulcus tissue but atrioventricular muscular connexions were not identified. Accessory atrioventricular conducting tissue was identified in atrial myocardium at the tricuspid orifice in over 20 per cent of hearts, but again did not make atrioventricular connexions. Accessory atrioventricular connexions were identified in 6 of the 8 hearts with pre-excitation. Seven connexions were identified. Four were discrete bundles which skirted the mitral anulus without perforating it. One was a right septal connexion and another perforated the tricuspid anulus. The final connexion originated from the anterior segment of the accessory atrioventricular ring conducting tissue.

### What is role of clinical electrophysiology in evaluation of patients with sinoatrial disease?

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Clinical recognition of sinoatrial (SA) disease currently depends on the demonstration of transient sinus bradycardia, sinoatrial block, or supraventricular tachyarrhythmias. The value of clinic electrophysiological assessment in these patients is not clear. Using intracardiac electrophysiological recordings and programmed stimulation we have evaluated 22 patients with sinoatrial disease and 12 control patients undergoing investigation for chest pain.

Intracardiac conduction times (AH and HV intervals) were normal in all patients. Effective atrial refractory periods and sinus node recovery times were not significantly different in the two groups of patients.

Two populations of sinoatrial conduction time were identified (with or without rate correction) but the mean values of 128 ±27 ms in patients and 112 ±30 ms in controls were not significantly different and major overlap rendered this measurement clinically valueless.

Sinus node or atrial re-entry was observed in 15 of 22 patients with SA disease (68%) and consisted of single or multiple re-entry beats and sustained tachycardias. Only 2 of 12 control patients showed re-entry phenomena.

It is concluded that no current electrophysiological measurement has diagnostic value in patients with sinoatrial disease. Re-entry activity can be shown in 68 per cent of patients with sinoatrial disease.

## Role of autoregulation in transmural distribution of coronary flow in canine left ventricular wall

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The distribution of blood to deep and superficial layers of the left ventricular wall is approximately equal in spite of a systolic pressure gradient favouring the superficial layers. It is believed that this homogeneity is achieved by autoregulation; relative ischaemia of deep layers causing vasodilatation such that any systolic flow deficit is made up in diastole. We tested this hypothesis in a canine preparation in which coronary flow could be varied independently of aortic pressure. Flow distribution to the left ventricular wall was measured by the microsphere technique. We found that partial or complete abolition of autoregulation by ischaemia, dipyridamole or adenosine had no effect on transmural flow distribution. This suggests that coronary flow must be virtually arrested in systole and be confined to diastole when pressure conditions favour equal distribution. As previously reported, a rise in ventricular diastolic pressure is associated with reduction of subendocardial flow. At low left atrial pressures, flow distribution is determined by the ratio of coronary diastolic pressure to ventricular systolic pressure. A fall in this ratio, however caused, results in relative underperfusion of deep muscle layers.

## $^{125}$I—Labelled fibrinogen, autoradiography, and stereoarteriography in identification of coronary thrombotic occlusion in fatal myocardial infarction

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The classical concept that acute coronary thrombotic occlusion is causally related to acute myocardial infarction has been challenged by recent observations. The evidence that thrombosis, when present, is commonly a sequel to infarction lacks validation.

In a prospective research programme, clinical data are correlated with evidence obtained from postmortem stereoarteriography of the heart and of excised coronary arteries and from serially mounted 2 mm transverse sections of the coronary arteries. Each patient had received 100 μCi $^{125}$I-labelled radiofibrinogen IV shortly after the onset of the acute ischaemic illness. Incorporation of radioactivity in thrombi was studied by autoradiography of the 2 mm serial sections. The technique is described, observations illustrated, and problems in interpretation discussed.

By December 1975, 25 cases were examined and preliminary results are reported. In nearly all acute regional infarcts, thrombus was found in the subtending artery. The portion of thrombus evidently causing occlusion was characteristically radionegative, suggesting formation before radiofibrinogen administration. Radiopositive thrombus was common at either end of the occlusive thrombus, in keeping with the thrombus formation after infarction. Occasionally, however, occlusive thrombus was radiopositive throughout.

The results mainly support a causal role for coronary occlusive thrombus in the pathogenesis of myocardial infarction.

## Unusual electrocardiographic response to exercise in patients with mitral leaflet prolapse

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Patients with mitral leaflet prolapse (MLP) often experience chest pain. Their investigation may include exercise testing to establish whether coronary artery disease (CAD) is present.

The response to electrocardiographically monitored submaximal exercise stress testing has been studied in 44 patients with MLP. With exercise ventricular ectopics occurred in 7, ventricular tachycardia in 1, and atrial fibrillation in 1. Exercise was terminated short of target heart rate in 18, because of chest pain (5), fatigue (7), ventricular arrhythmia (4), dizziness (1), or ST depression (1). Twenty-three patients developed post-exercise ST abnormalities, of whom 5 had 'ischaemic' patterns and angiographically proven CAD; among the 18 others, the ST segments were depressed and minimally downsloping in 2, slowly ascending from depressed J point in 3, horizontal for >80 ms with J depression of <1 mm in 12, and cupped in 1. In those without CAD the ST abnormality was either evanescent (not seen beyond 2 min post-exercise, 8 cases) or long-lasting (present at >8 min post-exercise, 10 cases).

Post-exercise ST abnormalities occur in patients with MLP without coexisting CAD (18/39, 46%) and have features which should be helpful in distinguishing from the progressively resolving ST deviation characteristic of CAD with angina.

## Natural history of ventricular arrhythmias during acute myocardial infarction

M. F. Oliver, M. J. Rowe, J. M. M. Neilson, A. Murray, and M. Taylor
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The variability and paroxysmal nature of ventricular arrhythmias during acute myocardial infarction makes their prevalence and prognostic significance difficult to assess.

Continuous electromagnetic tape recording of the electrocardiogram was started within 12 hours of the onset of symptoms in 28 patients with acute myocardial infarction and continued for 60 hours. A special hybrid computer was subsequently used to locate all ventricular premature beats (VPB) and to subdivide these into R on T ectopic beats and R on apex T ectopic beats. Slow and fast ventricular tachycardias were also differentiated by the computer. Antiarrhythmic drugs were not given to the patients.

The incidence and time of occurrence of the following ventricular arrhythmias have been precisely determined: (1) ventricular tachycardia, (2) R on T VPB on a preceding sinus beat, (3) R on T VPB on a preceding VPB, (4) R on apex T of a sinus beat or VPB.

An independent retrospective study of 3410 patients admitted to the Coronary Care Unit with myocardial infarction identified 81 with primary ventricular fibrillation (VF). The distribution of ventricular fibrillation by time is also described.

Primary VF is rare beyond four hours after the onset of symptoms, while the so-called 'serious' ventricular arrhythmias, outlined above, are common and persist for many hours. The apparent independence of VF from these other arrhythmias raises questions concerning the indications and effectiveness of antiarrhythmic drugs in the management of myocardial infarction.

## Effects of tachycardia and isoprenaline on coronary blood flow: observations on pathogenesis of myocardial infarction

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The Institute of Cardiology and the National Heart Hospital

Five anaesthetized open-chested mongrel dogs have been studied by measuring left anterior descending (LAD) coronary blood flow, left ventricular and aortic pressure with catheter-tip manometers, and epicardial electrograms.

After control measurements of pressures, LAD blood flow, and electrograms, the dogs were paced to a heart rate of 300 per minute, and then after termination of pacing were infused with isoprenaline until a similar heart rate was reached. The LAD was then stenosed in order to reduce the hyperaemic response from the resting value of 3·3:1 to a value of 1·5:1 and then the study was repeated.

During the control situation LAD flow was shown to increase with the increase in heart rate when either pacing or isoprenaline was used as the stress. Though the partial occlusion did not reduce resting coronary flow, this fell under stress conditions to 65 per cent of the control resting values. The importance of this observation is that though one might expect flow in a stenosed vessel to increase to a maximum limited by the stenosis, this in fact does not happen. It appears that with increasing stress, local ischaemia produces a rise in coronary resistance which reduces available flow below resting values. Such a mechanism may explain the occurrence of myocardial infarction without proximal occlusion of coronary vessels and may explain the discrepancy between the time course of myocardial infarction as seen after experimental coronary ligation and that seen in man.

### Rhythm of normal human heart

Joan M. Clarke, N. A. J. Hamer, J. R. Shelton,
Sue Taylor, and G. R. Venning
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Ltd., Lane End Road, High Wycombe, Bucks

The 24-hour cardiac rhythm was studied in 86 subjects (41 male and 45 female) aged 16 to 65 years, from a total of 101 volunteers from the employees of the company, after excluding the 16 with abnormalities in the medical history, physical examination, electrocardiogram, and biochemical and haematological screening. Each subject's electrocardiogram was recorded continuously for two 24-hour periods with a Holter recorder, and the tapes analysed using the Avionics Electrocardioscanner. The accuracy of the scanning procedure was established by visual inspection of a 60-minute sample in each of 21 representative subjects.

In this apparently normal population over a third showed abnormalities of rhythm, including many thought to be of serious prognostic significance, such as junctional rhythm, second degree heart block, frequent ventricular ectopic beats, R-on-T and multifocal ventricular ectopic beats, bigeminy and ventricular tachycardia. Brady- and tachyarrhythmias and conduction disturbances occurred similarly in waking hours and during sleep. Abnormalities were not confined to the older age groups. Heart rates were significantly higher in smokers and at expected times of activity during the day.

Data on normal variation are important in evaluating the significance of arrhythmia and drug treatment in coronary heart disease and the prevention of sudden death.

### Significance of cycle length alternation during drug treatment of supraventricular tachycardia

P. V. L. Curry and D. M. Krikler
Royal Postgraduate Medical School, London

Cycle length alternation (CLA) is commonly seen during an otherwise regular supraventricular tachycardia (SVT) before termination of attacks by drugs like verapamil which act mainly on the atrioventricular (AV) node. Characteristically, anterograde conduction time (P'Q or A'H) lengthens variably, usually progressively on alternate cycles, while retrograde times (QP' or VA') remain almost constant throughout; rarely is the converse seen.

Intracardiac studies in 16 patients with CLA invariably revealed a re-entry AV tachycardia involving either two intranodal pathways (one case) or one intranodal path with a partial (four) or complete (eleven) AV nodal bypass. There were pronounced differences in functional properties (conduction time, functional refractoriness [particularly in SVT] and paced second degree AV or VA block) between the pathways, especially in sensitivity to cycle length change and to verapamil (0·145 mg/kg iv), thus providing a mechanism whereby CLA can occur. This has been confirmed in normal subjects using a new technique; simulated AV re-entry tachycardia.

When CLA that varies is seen on the electrocardiogram during SVT, this strongly suggests a re-entry mechanism and, where atrial (P) and ventricular (QRS) events are clear, permits useful qualitative assessment of pathway properties.

## *Correspondence*

*British Heart Journal*, 1976, **38**, 883–884.

# Escape - capture bigeminy caused by blocked atrial extrasystoles

Sir,

Dubb and Schamroth (1975, **37**, 890) state that three basic mechanisms for escape-capture bigeminy have so far been described. After enumerating these, they present 'a hitherto unrecognized mechanism', viz. blocked atrial extrasystoles. This mechanism has already been described by Weiss (1973).

In Dubb and Schamroth's case the T wave of the sinus beat only appears to be equiphasic since an upright ectopic P′ wave is superimposed upon it. This T wave is inverted and the inversion of T in the escape beat is only slightly greater. The T inversion in the escape beat has been labelled 'post-extrasystolic'. Post-extrasystolic T wave change is a primary change which occurs in *sinus beats* following extrasystoles, but not in escape beats following blocked atrial extrasystoles, since in the absence of contraction of almost empty ventricles, the pause is similar to that seen in a block with dropped beats, which are never associated with any T wave change in the following sinus or escape beats. Aberrancy, on the other hand, is quite common in escape beats. The escape beats in this case clearly show aberrant ventricular conduction, leading to an increase in amplitude of QRS in the lead illustrated. This must, of necessity, result in an increase in the T inversion as a secondary T wave change. Hence it is not a post-extrasystolic T wave change and is devoid of any pathological significance.

When escape-capture bigeminy results from a basic 3:1 sinoatrial block with escape beats, if the escape beat occurs *'coincidentally with'* the first sinus beat of the next ensuing 3:1 sequence as stated by the authors, the sinus beat will not be conducted to the ventricle; in the absence of capture of the ventricle by the sinus beat, there can be no escape-capture bigeminy. In order that escape-capture bigeminy may be possible with 3:1 SA block, the escape beat should *not be coincident with* but should *precede* the sinus beat at a sufficient interval, thus permitting the latter to capture the ventricle; *or* alternatively, the block ratio should be 3:2 and not 3:1.

Doctor Jamaluddin,
Sir Ganga Ram Hospital,
Lahore,
Pakistan.

### Reference

Weiss, I. W. (1973). *Essentials of Heart Rhythm Analysis*, p. 209. F. A. Davis, Philadelphia.

This letter was shown to Dr. Dubb and Professor Schamroth who reply as follows:

Sir,

We would like to express our appreciation to Dr. Jamaluddin for his interest in our paper 'Escape-capture bigeminy caused by blocked atrial extrasystoles', and to thank him for drawing our attention to his observation that the mechanism had already been described by Weiss. We were unaware of this, and are still unable to obtain the book.

Dr. Jamaluddin is incorrect in stating that 'the T wave of the sinus beat only appears to be equiphasic since an upright ectopic P′ wave is superimposed upon it'. The ectopic P′ wave is superimposed on the proximal part of the ST segment and is well clear of the T wave; as is quite evident in the tracing. The T wave is obviously inverted in the escape beat, and thus differs significantly from the equiphasic T wave of the conducted sinus beat. The T wave change of the escape beat is, therefore, a true, so-called 'post-extrasystolic' T wave change. Dr. Jamaluddin is further incorrect in stating that these T wave changes are never associated with block. Indeed, it was Scherf (1944) who originally indicated that the change is not the result of the extrasystole as such, but rather of the pause which it evokes. It may thus be associated with any sudden long pause such as occurs with blocked atrial extrasystoles or following the relatively long ventricular cycles in atrial fibrillation.

We do not understand Dr. Jamaluddin's reference to, 'the absence of contraction of almost empty ventricles'. Furthermore, we very much doubt whether the escape beats clearly show aberrant ventricular conduction, as he states. The slight change in amplitude of the QRS complex could be a positional effect resulting from overfilling of the ventricles, and was not evident in other leads. However, even if this change is indeed aberration, it is so slight that it could not account for the real inversion of the associated T wave.

Dr. Jamaluddin is correct in pointing out that with a basic 3:1 sinoatrial block, escape capture bigeminy cannot occur when the escape beat occurs coincidentally with the first sinus beat of the next ensuing 3:1 sequence, as was stated in our text. He correctly points out that the escape beat must precede the next conducted sinus beat. We very much regret this momentary aberration on our part.

A. Dubb,
L. Schamroth,
Baragwanath Hospital,
P.O. Bertsham,
Johannesburg,
South Africa.

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Scherf, D. (1944). Alterations in the form of the T waves with changes in heart rate. *American Heart Journal*, **28**, 332

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# British Heart Journal

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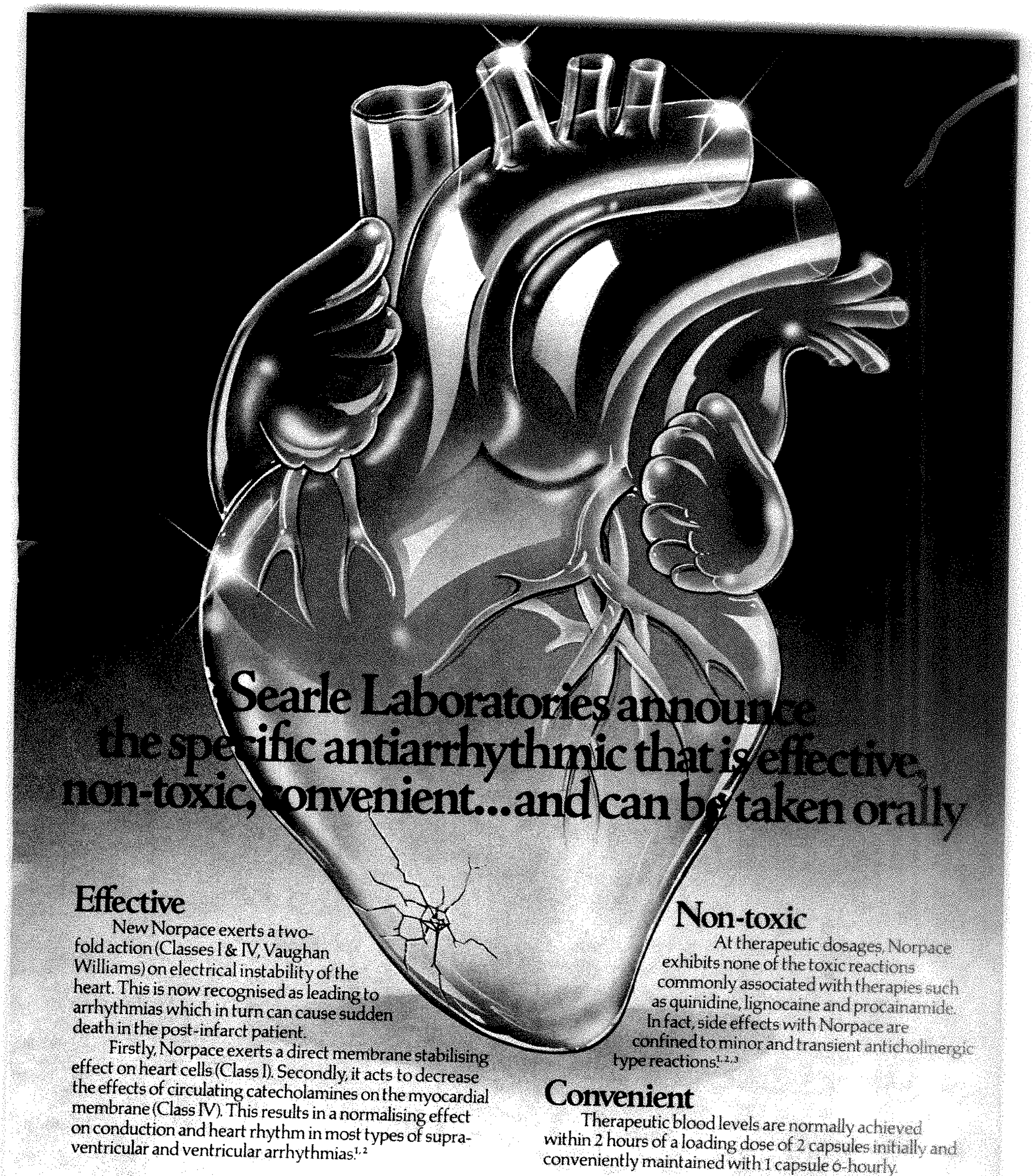

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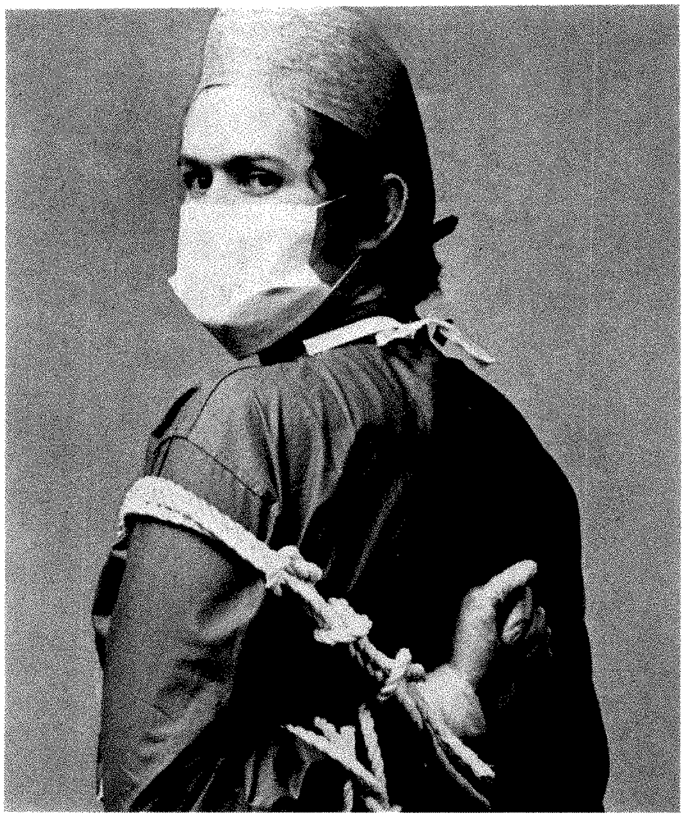

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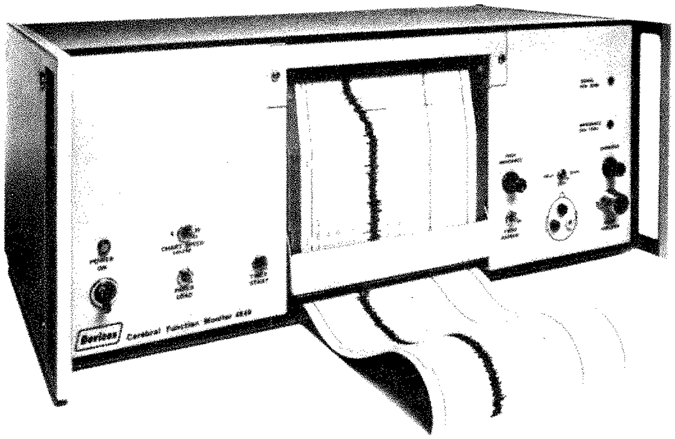

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58
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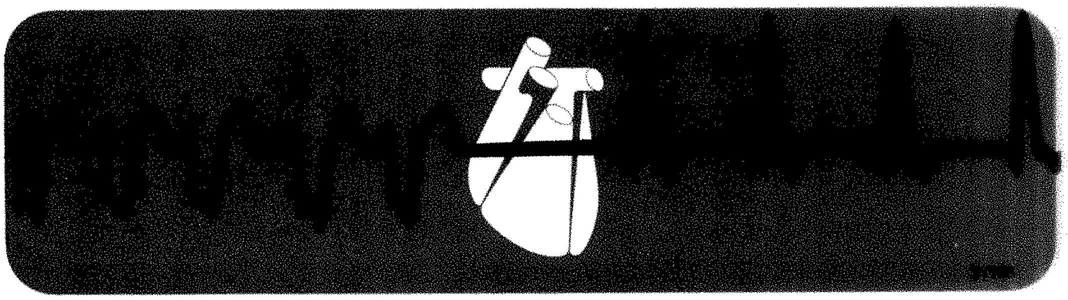

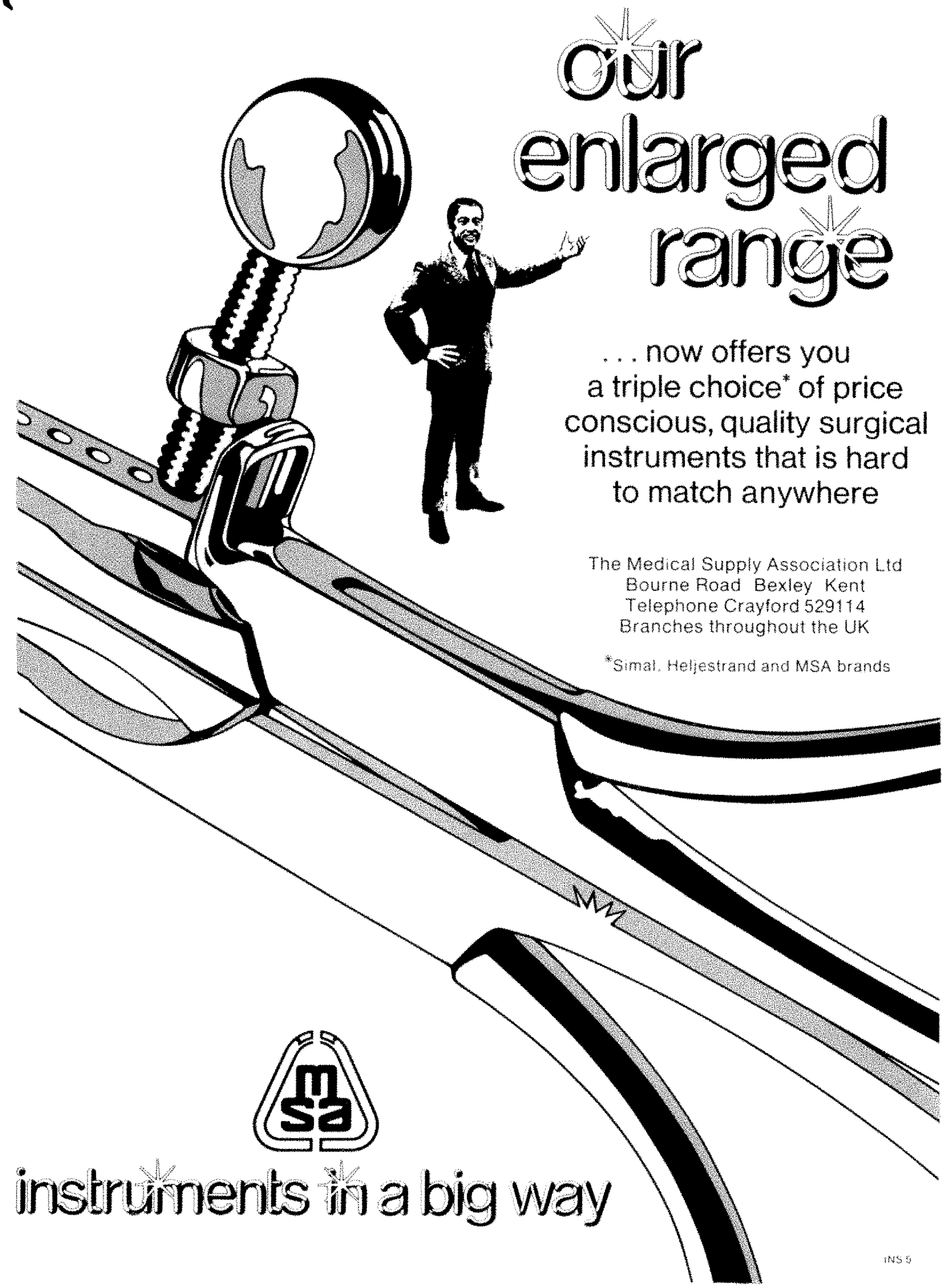

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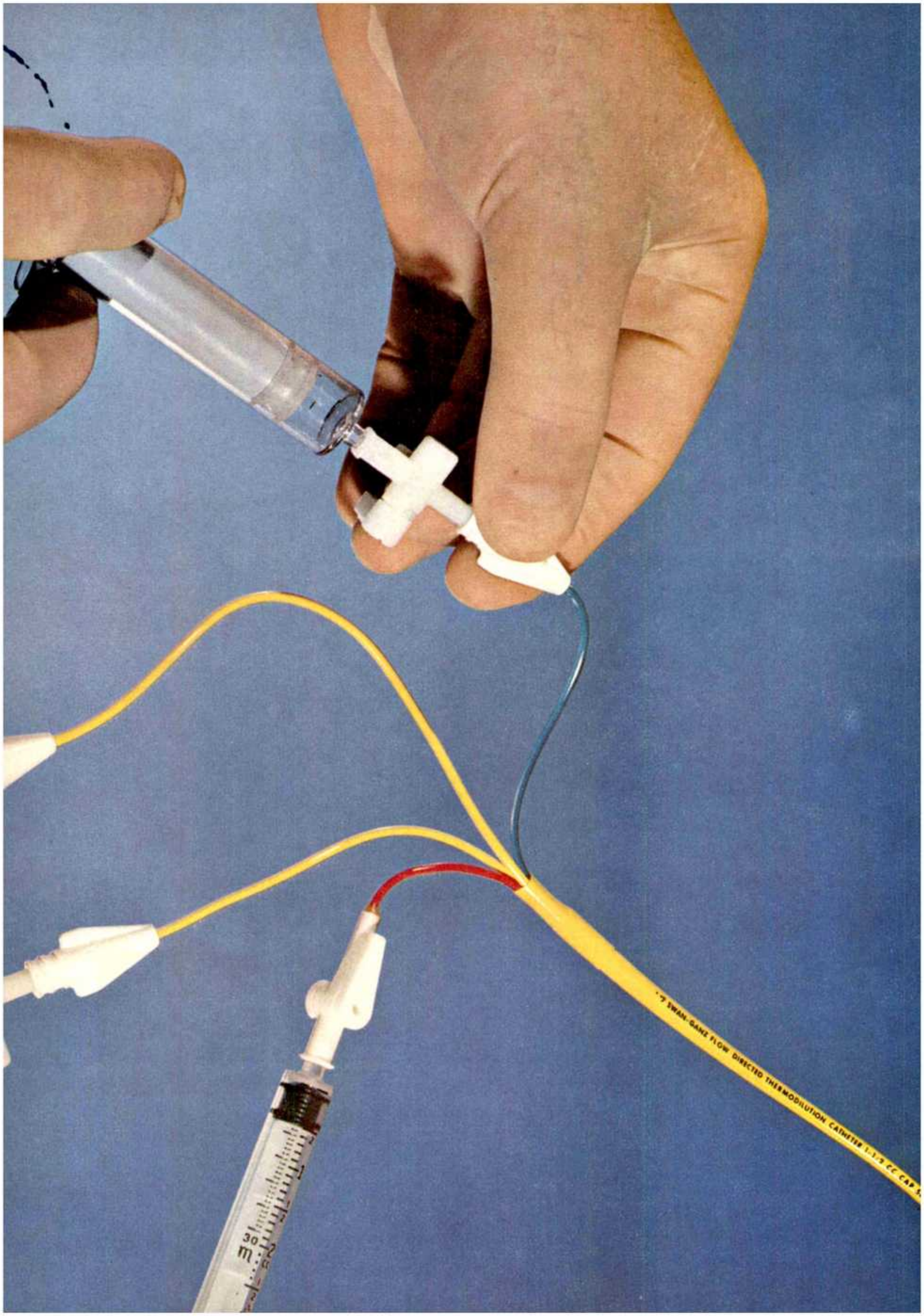
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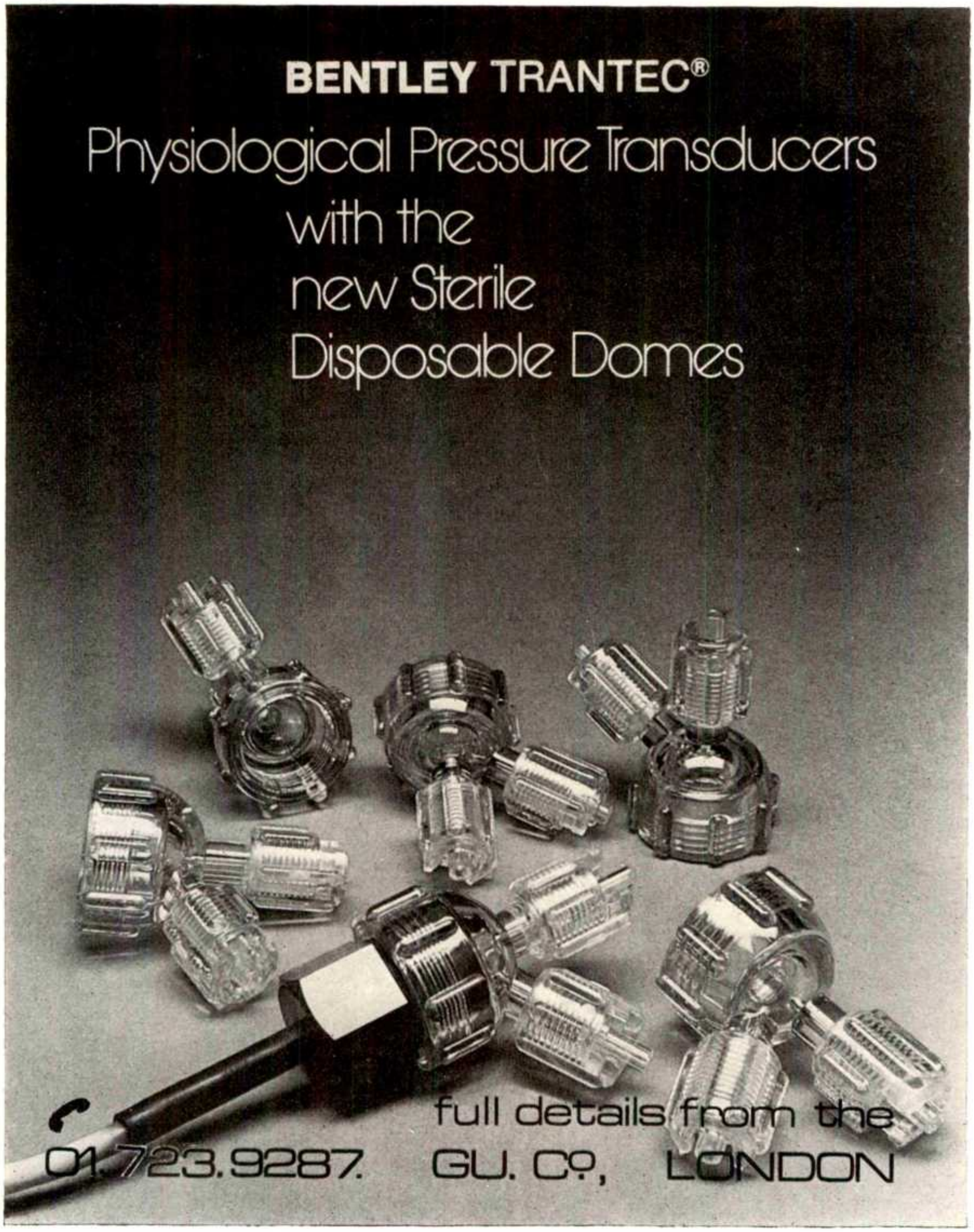

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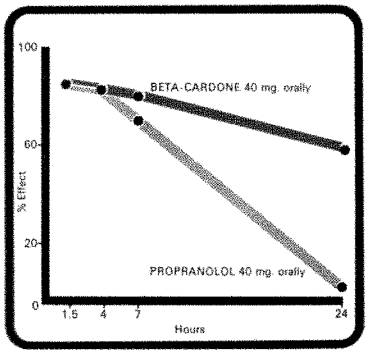

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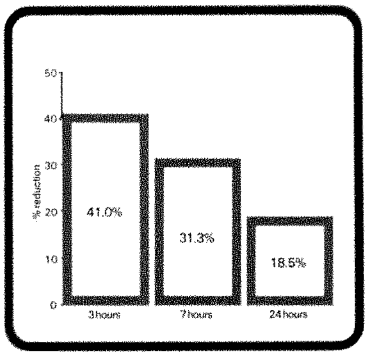

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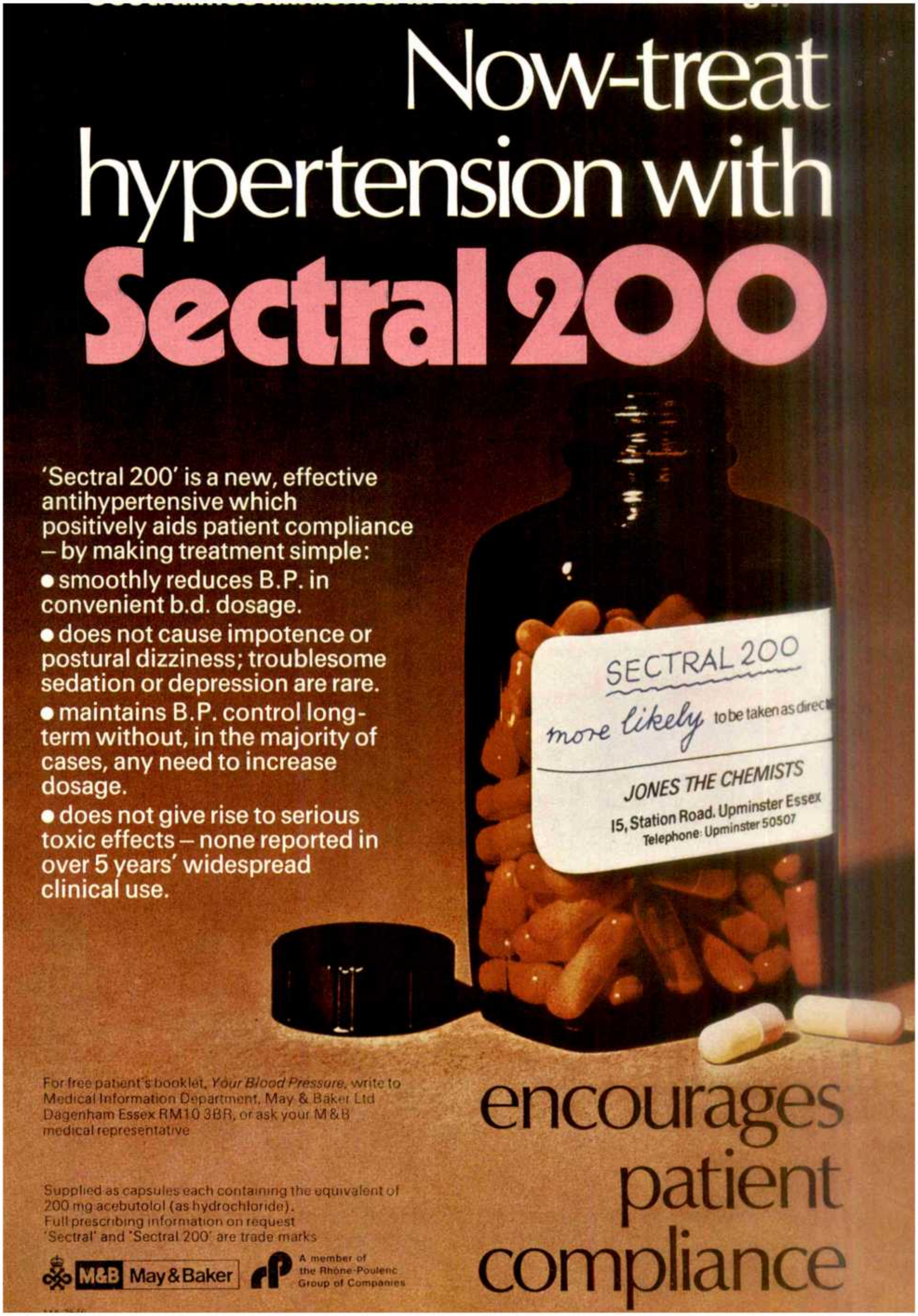
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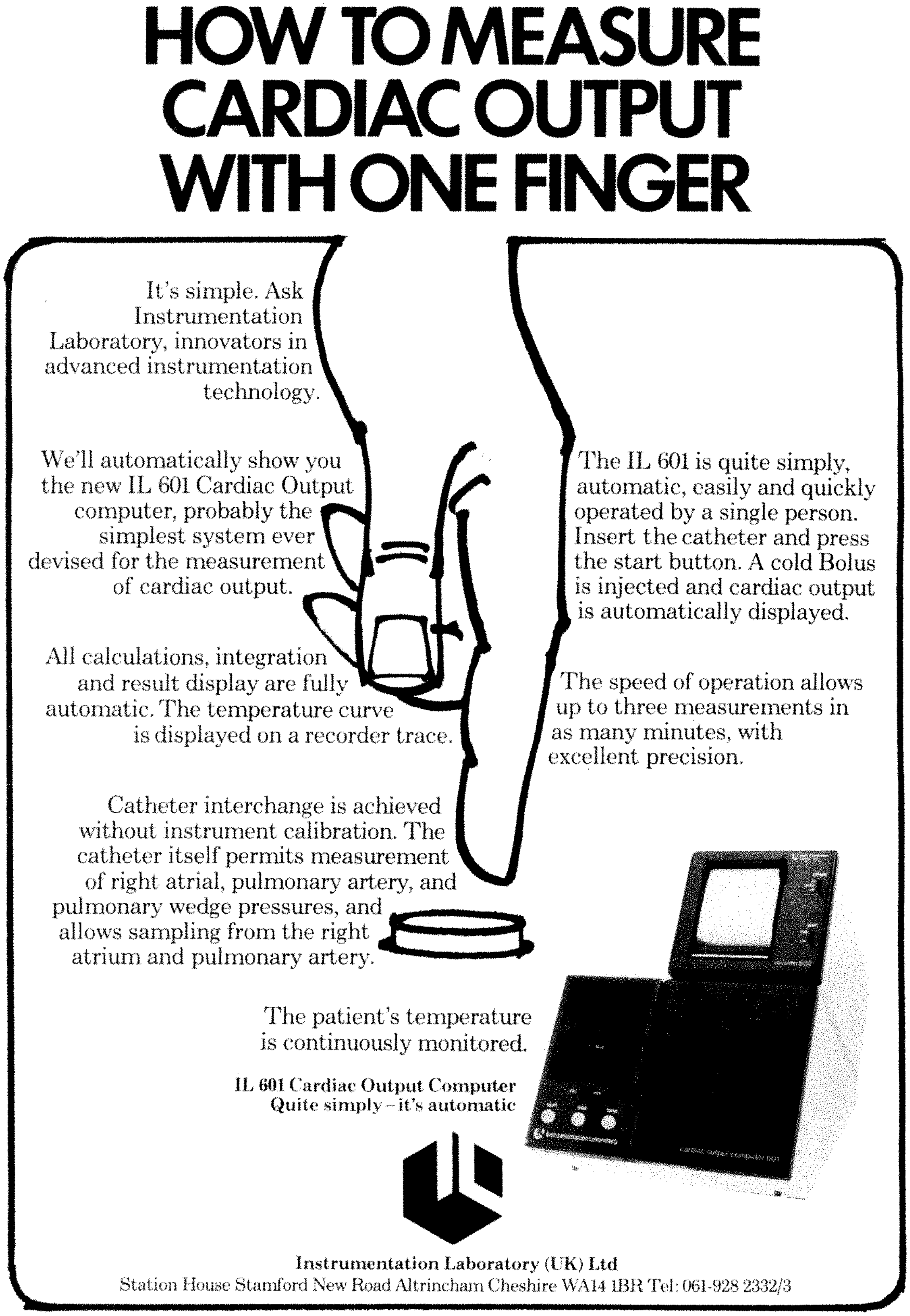

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# 'Incessant' tachycardias in Wolff-Parkinson-White syndrome[1]

## *I: Initiation without antecedent extrasystoles or PR lengthening, with reference to reciprocation after shortening of cycle length*

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*In 6 patients with the Wolff-Parkinson-White (WPW) syndrome, repetitive, almost continuous (incessant) reciprocating atrioventricular (AV) tachycardia has been shown to arise when the sinus cycle length was shortened to a critical point, at which unidirectional block occurred without the classical feature of PR prolongation. Though this phenomenon superficially resembles an aspect of chronic intranodal reciprocating tachycardia of children, basic differences can be identified. It was encountered more frequently in younger subjects; the only patient over 45 developed the arrhythmia as a complication of therapy. This incessant mechanism may explain some cases in which antiarrhythmic treatment does not control reciprocating tachycardia in the WPW syndrome, but such a mechanism can also occur spontaneously.*

Reciprocating atrioventricular (AV) tachycardias, whether involving the AV node alone or in association with an extranodal bypass, depend on the existence of two separate functional (or anatomic) pathways which can constitute a circuit that permits reciprocation—the persistent transmission of an impulse anterogradely in the one direction and retrogradely in the other. Classically, such tachycardias are initiated by extrasystoles that induce anterograde block in one pathway, with PR prolongation, and occur in the form of intermittent episodes of varying duration, usually infrequently, but sometimes sufficiently often to be labelled repetitive (Parkinson and Papp, 1947). It is only recently that a specific 'incessant' form of reciprocating AV nodal tachycardia has been recognized and its features clarified (Coumel *et al.*, 1967; Coumel, 1975). This arrhythmia tends to affect children rather than adults, classically shows inverted P′ waves in leads II, III, and a VF (with RP′ longer than P′R) and is initiated *not* by PR prolongation but by a critical shortening of the PP interval in sinus rhythm. We have now recognized that this last mechanism, viz. critical shortening of the PP interval, can induce reciprocating tachycardia in the Wolff-Parkinson-White (WPW) syndrome, especially, though not invariably, in response to the administration of various antiarrhythmic agents, and this report describes 6 cases that illustrate its features. Electrophysiological studies were carried out by recognized techniques of intracardiac recording and programmed stimulation (Curry, 1975), the patients or their guardians having given consent after proper explanation; sedation was not used and all medications had been discontinued for at least 72 hours before investigation.

### Case reports

#### Case 1

A 2-year-old child suffered from intractable paroxysmal supraventricular tachycardia that occurred in incessant or apparently self-limiting attacks (Fig. 1), either spontaneously or brought on

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by febrile illnesses. During sinus rhythm, the pattern of WPW conduction (Fig. 1) was usually absent. It was not possible to initiate supraventricular tachycardia by premature atrial or ventricular stimulation. Isoprenaline was then administered intravenously, and the initiation of attacks of tachycardia without antecedent PR prolongation is shown in Fig. 1; in Fig. 2 (in which the WPW pattern is now seen) this is confirmed and the tachycardia is seen to restart after very subtle

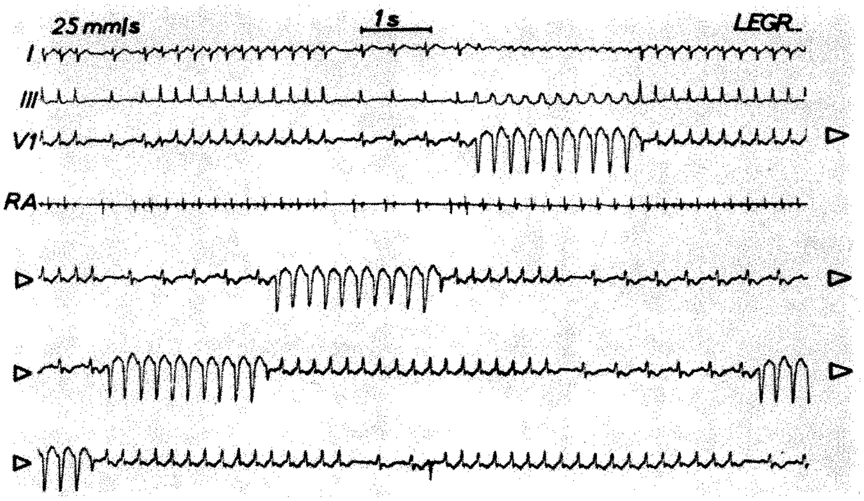

FIG. 1 *Case 1: recorded after the intravenous administration of isoprenaline shows three surface leads and a right atrial electrogram (RA). The third, fifth, sixth, and seventh tracings are continuous recordings of V1. Short paroxyms of tachycardia are seen to end spontaneously but to recur after two or more sinus beats; the PR intervals of the sinus beats immediately preceding the onset of tachycardia are not prolonged. In most instances, the first 7 to 10 beats of the tachycardia show QRS widening caused by left bundle-branch block which does not influence the rate of the tachycardia.*

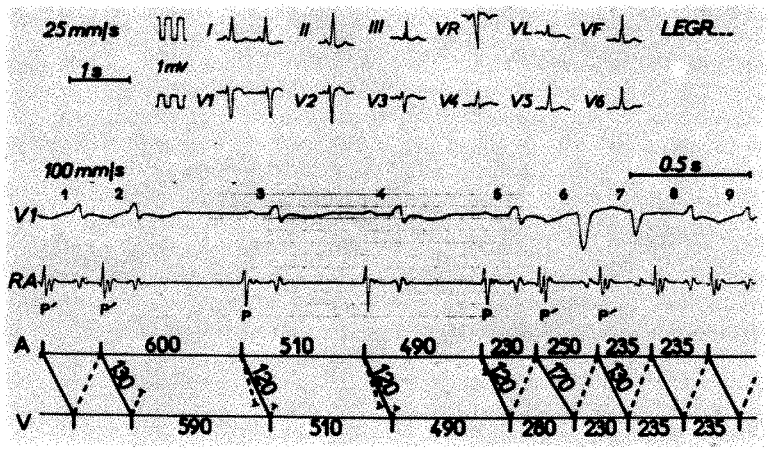

FIG. 2 *Case 1: the upper panel is a standard 12-lead electrocardiogram recorded one week before the study, showing the presence of the WPW syndrome type B (chest leads recorded at half voltage). The lower panel shows the same phenomenon as in Fig. 1, but displayed at faster paper speed: the PR interval in the third, fourth, and fifth beats is 120 ms, the P4-P5 interval being 20 ms shorter than the P3-P4 interval. The first RR interval in tachycardia (280 ms) was longer than the subsequent ones (235). In the right atrial electrocardiogram P and P′ are used synonymously with A for atrial activation.*

shortening of the cycle length in sinus rhythm. The first RR interval of tachycardia is relatively long (280 ms) and then becomes shorter. A likely explanation for failure of initiation of tachycardia by beats 3 and 4 (Fig. 2) is concealed anterograde conduction within the accessory pathway, but this is absent in beat 5 because of the shortening of the relevant PP interval.

**Case 2**

This patient was an 18-year-old boy with intermittent type A WPW syndrome associated with frequent attacks of reciprocating supraventricular tachycardia since the age of 1 year. While at first vagal manoeuvres often terminated the episodes, recently the attacks had occurred so frequently that half his waking day was spent in tachycardia.

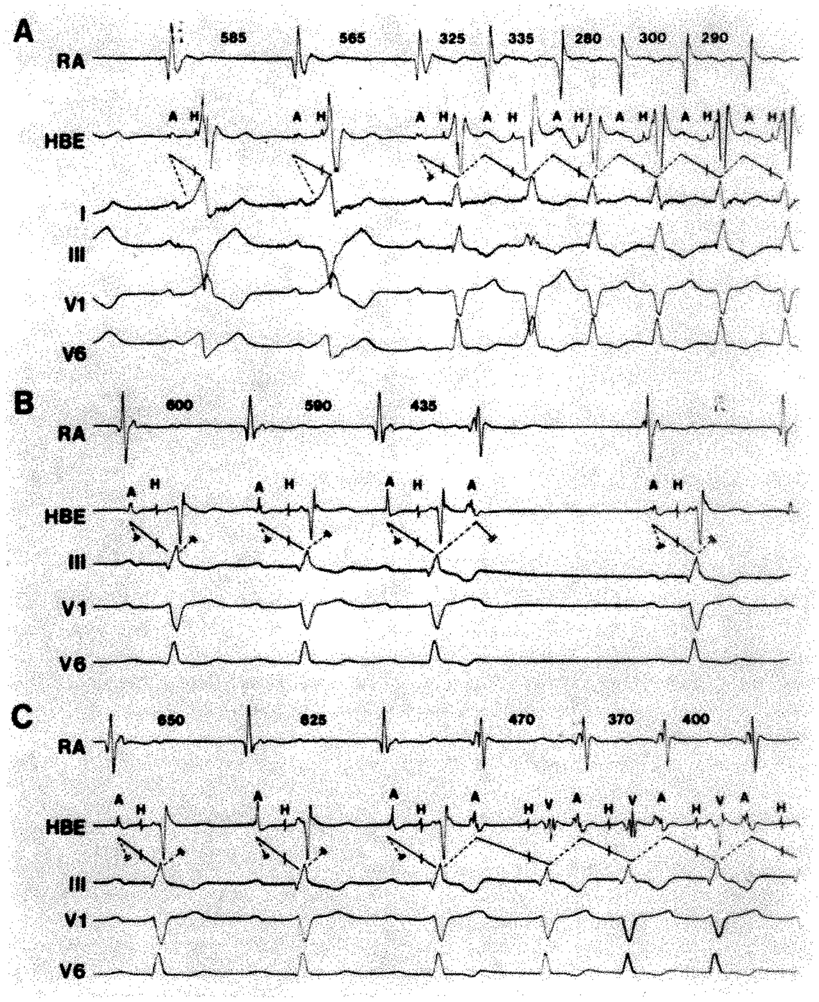

FIG. 3 *Case 2: right atrial (RA) and His bundle (HBE) electrograms recorded simultaneously with leads I, III, V1, and V6. (A) There is a pre-excitation pattern in the first two complexes, with gradual shortening of the cycle length to 565 ms: tachycardia with narrow QRS complexes is initiated by the third complex. (B) Sinus rhythm, after intravenous ajmaline and verapamil: no evidence of pre-excitation; the third beat is followed by a spontaneous atrial echo which does not initiate tachycardia. (C) Soon after (B): the first three beats are sinus in origin, the third being followed by an atrial echo which now initiates tachycardia. Note that in both (A) and (C), the first RR interval in tachycardia was longer than those in subsequent cycles.*

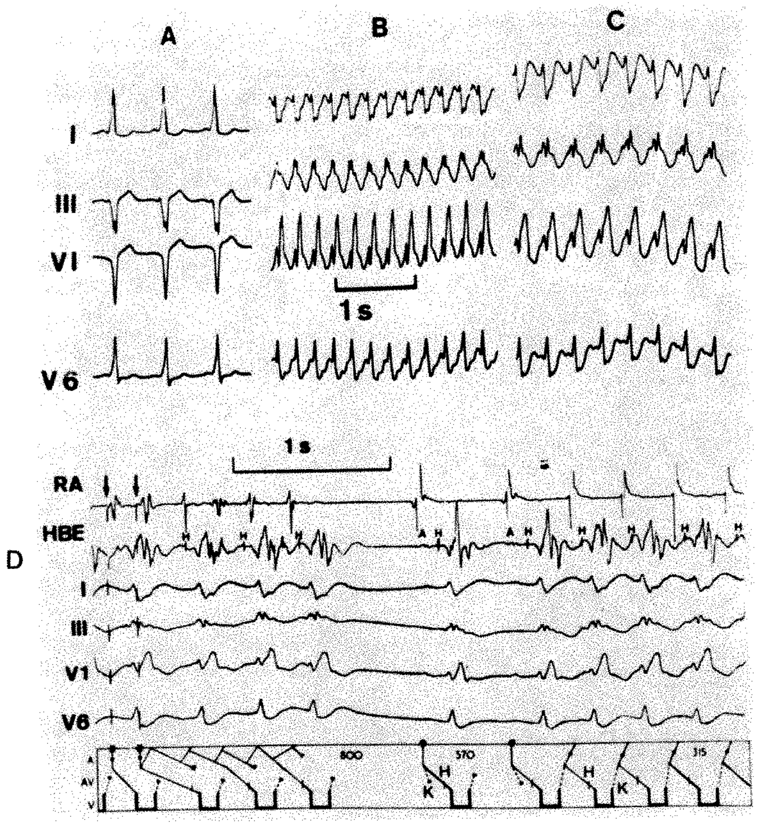

FIG. 4 *Case 3: panels A, B, and C: electrocardiograms (leads I, III, V1, and V6). H=His bundle; K=bundle of Kent. (A) WPW syndrome type B. (B) Reciprocating tachycardia (240/min), with RBBB. (C) Same as in (B), but after ajmaline, showing slower rate (180/min) with additional QRS widening. (D) Intracardiac and surface electrocardiograms, after ajmaline: after two atrial premature beats introduced during the tachycardia, a localized irregular atrial tachycardia developed as the reciprocating tachycardia terminated; the two subsequent beats are sinus in origin, showing no evidence of anterograde bypass conduction, but are conducted with RBBB. Tachycardia starts after the second sinus beat at a critical and reproducible PP interval of 570 ms but without previous lengthening of the anterograde conduction time (AH=120 ms).*

Many attacks were initiated at the onset of physical activity, as was confirmed during an exercise test.

At the start of the study there was one spontaneous attack of tachycardia (Fig. 3A) but this occurred more consistently and repeatedly once he had received intravenous ajmaline (0·75 mg/kg body weight); when these were stopped with electric stimuli, only a few sinus beats followed before another episode of tachycardia ensued (Fig. 3C). After the addition of verapamil (0·15 mg/kg body weight) only one or two abortive atrial echo beats occurred (Fig. 3B). Once ajmaline had been given, there was anterograde bypass block, with no evidence of pre-excitation (Fig. 3B and C), and anterograde bypass conduction did not return during the rest of the study. It was then possible to stop the incessant state completely using a larger dose of verapamil (totalling 0·3 mg/kg body weight), and one hour after the study, when the effect of the drugs had worn off, sinus rhythm was maintained.

Subsequently it has proved possible to suppress his tachycardia with verapamil, 400 mg, and long-acting quinidine, 2000 mg, a day, so that he now has attacks infrequently (once or twice a month) and for brief periods, despite active physical work.

## Case 3

A 42-year-old man had suffered from increasingly frequent attacks of reciprocating supraventricular tachycardia for 3 years: electrocardiogram showed the WPW syndrome type B (Fig. 4A). He invariably showed right bundle-branch block during the reciprocating tachycardia, and in sinus rhythm when the bypass was blocked by ajmaline (Fig. 4B, C, and D). Incremental atrial pacing up to a rate of 220/min failed to initiate tachycardia, but this was induced by single atrial extrastimuli in the range of 290 ms after the last preceding driven beat; the effective refractory period of the bypass was 290 ms and of the AV node, 270 ms.

He was then given ajmaline intravenously (0·75 mg/kg body weight). During the 20 minutes in which its effects persisted, it was impossible to suppress tachycardia for more than a few seconds; thereafter he lost the incessant tachycardia. As can be seen in Fig. 4D, the tachycardia was not preceded by any lengthening or anterograde conduction through the AV node, but started after shortening of the PP intervals to a critical point.

Subsequently he has remained free from tachycardia on verapamil 160 mg and long-acting quinidine 1000 mg a day.

## Case 4

A 31-year-old man presented with recurrent reciprocating tachycardia of 4 years' duration. Electrocardiogram (Fig. 5A) showed the WPW syndrome type B. His typical tachycardia pattern is shown in Fig. 5B; in Fig. 5C the tachycardia had been slowed by ajmaline. During an electrophysiological study, incremental right atrial pacing showed a delta wave, and at a rate of 220/min, anterograde conduction in the bypass failed, reciprocation initiating orthograde tachycardia with narrow QRS complexes; the refractory period of the bypass for anterograde conduction was 280 ms. After ajmaline (0·75 mg/kg body weight) intravenously, anterograde conduction down the bypass was blocked, and thereafter there were frequent spontaneous attacks of tachycardia by the incessant mechanism, without antecedent prolongation of anterograde conduction in the AV node (Fig. 6). During sinus rhythm, after ajmaline, the anomalous conduction was suppressed (Fig. 5D). When the effects of ajmaline were more pronounced (Fig. 6A and B), tachycardia was incessant and there was no anterograde bypass conduction; as these effects wore off, alternate beats were conducted anterogradely via the AV node and the bypass, and the tachycardia restarted less and less often, and finally could only be reinitiated by premature stimuli (Fig. 6C). He has responded well to prophylactic treatment with verapamil.

## Case 5

A 5-year-old boy had suffered from recurrent paroxysmal tachycardia since the age of 3 months. Electrocardiograms taken in infancy showed no evidence of pre-excitation (Fig. 7B) but at the age of 4, the WPW syndrome type B became evident intermittently (Fig. 7A), and the tachycardia, which had been almost permanent (Fig. 8B) occurred less often but was disabling at times. The spontaneous cessation of tachycardia is shown in Fig. 8A, with no obvious anterograde PR prolongation or shortening of PP intervals prior to the reinitiation of tachycardia. The incessant nature of the tachycardia can be seen from Fig. 8B, only occasional sinus beats separating runs of arrhythmia. During tachycardia

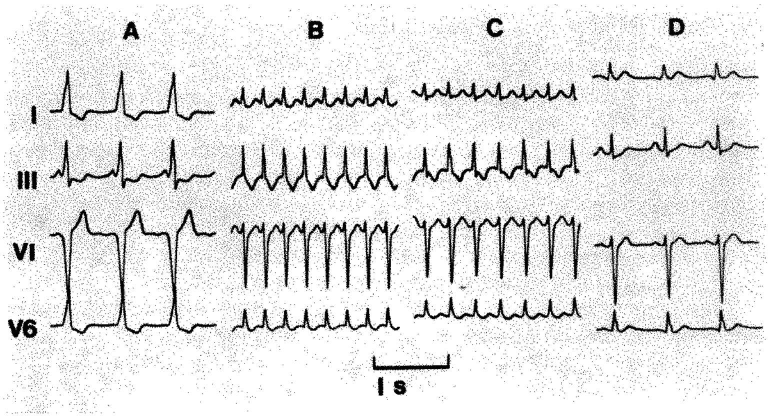

FIG. 5 *Case 4. Electrocardiograms leads I, III, V1, and V6. (A) Sinus rhythm with WPW syndrome type B (no medication). (B) Reciprocating tachycardia with narrow QRS complexes (215/min). (C) As in (B), rate slightly slowed by ajmaline (185/min). (D) A group of sinus beats after ajmaline, showing normalized conduction.*

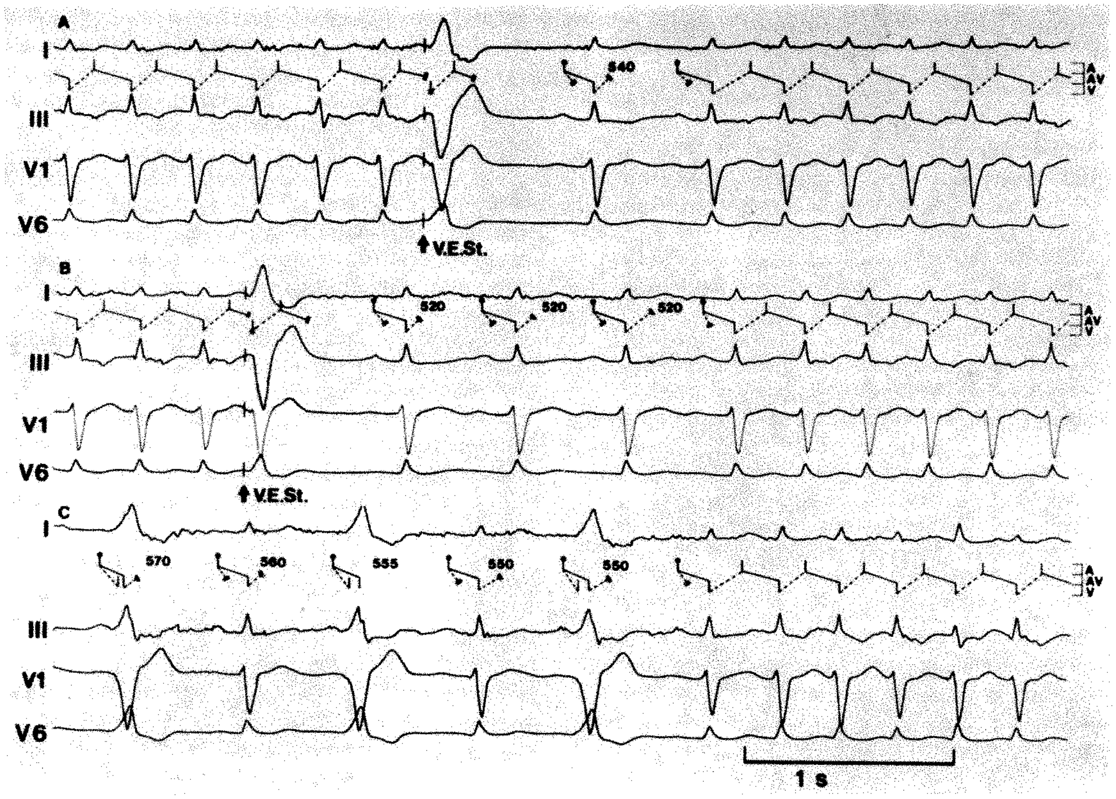

FIG. 6 *Case 4: Electrocardiograms (leads I, III, V1, and V6); (A) and (B) are within 10 minutes and (C) 15 minutes, after ajmaline. (A) Reciprocating tachycardia stopped by a ventricular extrastimulus; tachycardia reinitiated by the second of the subsequent sinus beats, neither of which showed pre-excitation. (B) As in (A), but tachycardia reinitiated by fourth sinus beat. (C) In sinus rhythm there is alternating nodal/bypass conduction, with reinitiation of tachycardia by a sinus beat with AV nodal conduction. Note that the first RR interval during tachycardia is longer than those in subsequent beats.*

with right bundle-branch block, the retrograde conduction time (RP′) was 160 ms, significantly longer than during left bundle-branch block complicating tachycardia (120 ms). This suggested the presence of a concealed right-sided bypass: with right bundle-branch block, the longer retrograde conduction time implied that the impulse had to travel further, to reach the unsuspected bypass, analogous to the situation seen when left bundle-branch block complicates reciprocating tachycardia in the presence of a left-sided bypass (Slama, Coumel, and Bouvrain, 1973; Spurrell, Krikler, and Sowton, 1974).

At electrophysiological study the presence of intermittent WPW syndrome type B was noted, but the bypass refractory period was long (over 600 ms) and it ceased to conduct anterogradely. The retrograde bypass refractory period was 280 ms, prolonged to 490 after ajmaline (0·7 mg/kg body weight). Tachycardias were initiated over a wide echo zone from atrial or ventricular extrastimuli; after ajmaline, the typical incessant pattern developed. The attacks have subsequently decreased in frequency and severity and he no longer requires prophylactic therapy.

## Case 6

A 58-year-old woman had suffered from disabling attacks of supraventricular tachycardia for 4 years. Electrocardiograms in sinus rhythm revealed no definite evidence of pre-excitation, but the PR interval was 0·12 s. She was referred because an attack of tachycardia had not responded to combined therapy with digoxin, lignocaine, and

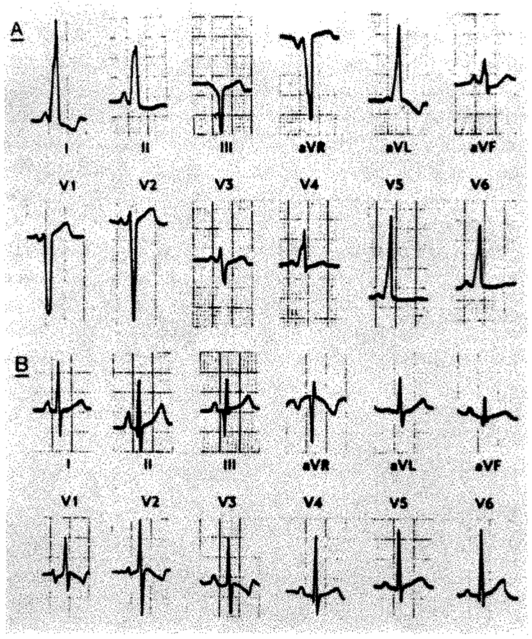

FIG. 7 *Case 5. Twelve-lead electrocardiograms. (A) WPW syndrome type B, taken at the age of 4. (B) Tracing taken in infancy, showing no pre-excitation.*

practolol (Fig. 9). As can be seen in Fig. 9b and c, the tachycardia stopped, but restarted as the sinus cycle length shortened. Electrophysiological study showed her to have a short AH interval as well as a left-sided bypass (bundle of Kent) as shown by the fact that, during induced tachycardia, the left atrium was depolarized 75 ms before the right (Fig. 10). The AH interval did not lengthen significantly on atrial pacing or with atrial extrastimuli, and thus had features compatible with a partial atrionodal bypass ('James' fibres), which may explain the rapidity of the tachycardia (Fig. 9a). As the tachycardia reverted to sinus rhythm after intravenous verapamil, the cycle lengths alternated (Spurrell, Krikler, and Sowton, 1973; Curry and Krikler, 1976). She has had no attacks while on verapamil 360 mg daily.

## Discussion

Classically, in junctional reciprocating tachycardia (AV nodal tachycardia), whether involving the AV node alone or as a feature of the WPW syndrome, the attacks are initiated by extrasystoles. The underlying prerequisite for the occurrence of a circus movement tachycardia is the presence of an available circuit in which the impulse can travel between atria and ventricles, and when the AV node alone is involved, the pathways are conventionally called α and β, reflecting differences in conduction velocity and refractory periods (Mendez and Moe, 1966; Janse *et al.*, 1971). For tachycardia to start, unidirectional block is required in the β pathway, and conduction must be slowed so that the impulse traversing the α pathway can return retrogradely via β and then encounter a no-longer-refractory α pathway so that the re-entry process can continue. Initiation of tachycardia has been shown to follow premature beats induced in the atrium or ventricle that enter the circuit and cause unidirectional block in the α pathway and slowed conduction; this is seen as prolongation of the PR interval at the start of the tachycardia (Coumel *et al.*, 1967, 1970; Goldreyer and Damato, 1971; Goldreyer, Weiss, and Damato, 1971; Wellens, 1971). The analogous mechanism has of course been shown to underly reciprocating tachycardias in the WPW syndrome; appropriately-timed atrial extrasystoles that are blocked in the anomalous pathway but conducted down the normal route characteristically initiate a circus movement

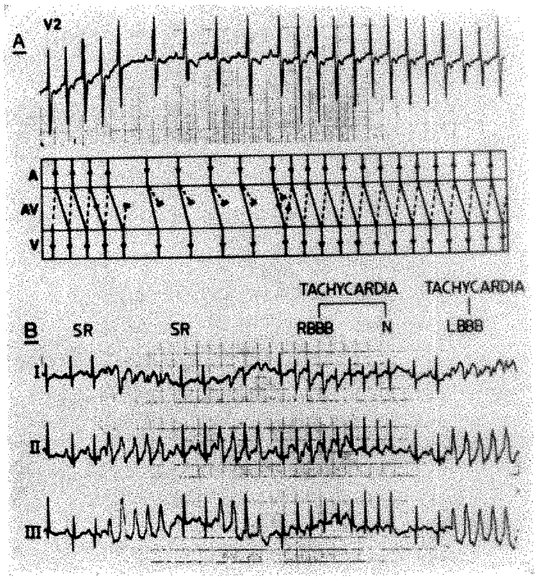

FIG. 8 *Case 5. (A) Cessation and resumption of tachycardia with normal intraventricular conduction. (B) Incessant tachycardia, with repetitive changes from sinus rhythm (SR) to tachycardia which showed normal intraventricular conduction (N) and right and left bundle-branch aberration (RBBB and LBBB). During RBBB the RP' interval was 160 ms, and during LBBB, 120 ms.*

tachycardia (Durrer *et al.*, 1967). Assessment of tachycardias initiated in this way is a fundamental investigation in the electrophysiological assessment of junctional reciprocating tachycardias (Wellens, 1971; Curry, 1975). The occurrence of appropriately-timed spontaneous extrasystoles is clearly an important factor in the occurrence of many cases of repetitive paroxysmal junctional tachycardias (Gallavardin, 1922; Parkinson and Papp, 1947; Krikler, 1974a).

Analysing conventional electrocardiograms, Katz and Pick (1956) and Kistin (1965) attributed repetitive paroxysmal tachycardia to a re-entry mechanism. Recognition of the characteristic electrocardiographic features of some repetitive tachycardias, with especial reference to their mode of initiation in that the unidirectional block of the pathway was produced by an increase in the heart rate rather than a suitably timed extrasystole (Coumel *et al.*, 1967), has led to the reappraisal of many reports of so-called focal left atrial tachycardia. This might be suggested by the relative closeness of the first P′ wave to the first QRS of tachycardia and the inverted P′ waves in leads II, III, and aVF (Von Bernuth, Belz, and Schairer, 1973; Kistin, 1965; Keane, Plauth, and Nadas, 1972); or there may be confusion with the usual mechanism for the initiation of reciprocating

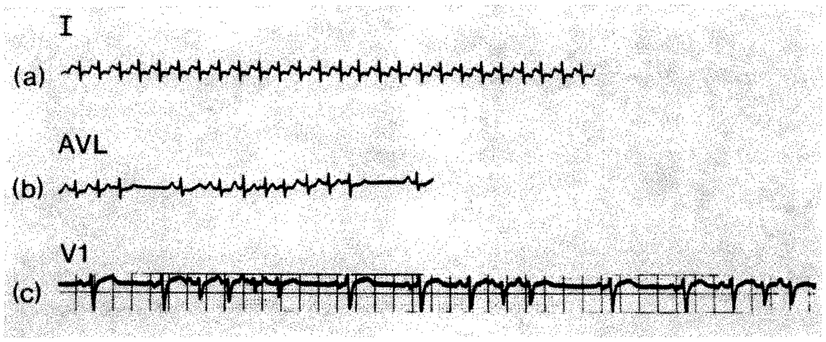

FIG. 9 *Case 6: Electrocardiograms recorded during tachycardia (a) before treatment (250/min). (b) and (c) under the influence of digoxin, practolol, and lignocaine: note cessation of tachycardia with reinitiation as the sinus cycle shortened, best seen in (c).*

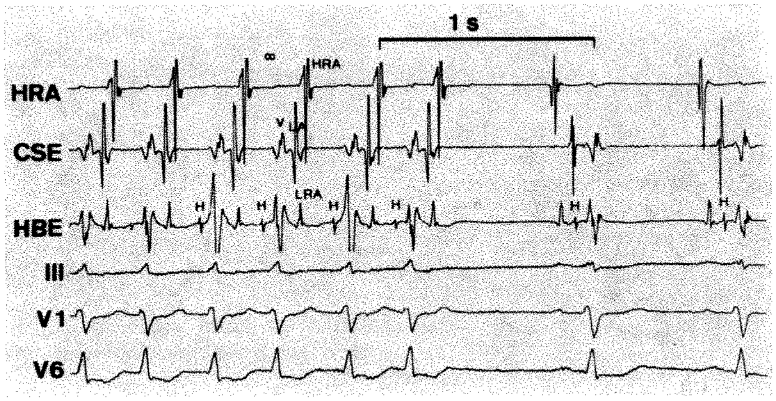

FIG. 10 *Case 6: Intracardiac and surface electrocardiograms, showing termination of tachycardia after intravenous verapamil. In tachycardia, the left atrium (LA in CSE) was depolarized 75 ms before the low right atrium (LRA in HBE); the normal atrial activation sequence is seen in the two subsequent sinus beats. AH=55 ms. CSE=coronary sinus electrogram.*

junctional tachycardia (Gettes and Yoshonis, 1970; Rosen, 1973). Using progressively accelerated atrial pacing, it is possible to show that a critical PP interval can be reached in order to initiate the tachycardia (Coumel *et al.,* 1974; Coumel, 1975). Castellanos and Myerburg (1975) may well be hinting at this mechanism when they indicate that conspicuous sinus arrhythmia may act like extrasystoles in inducing reciprocating AV tachycardia.

Our cases with pre-excitation differ in several important ways from these chronic intranodal tachycardias (Coumel, 1975). Most important, the P′R interval was always longer than RP′, instead of the converse, and RP′ was constant and uninfluenced by vagal or drug effects. The relatively short and constant RP′ in our present cases conforms with the use of a bypass tract retrogradely during tachycardia. Also, the first cycle length (RR) of tachycardia in Cases 1, 2, and 4 was longer than the cycle lengths in successive beats, by which time anterograde intranodal conduction had speeded in proportion to the heart rate; the first cycle length in the intranodal form is often shorter, in keeping with the presence of an initial common pathway. Classically, of course, the intranodal tachycardias originate in infancy and persist for long periods, even decades; we now, however, describe briefer, perhaps ephemeral, phenomena, usually drug-induced.

In assessing mechanisms of the initiation of incessant tachycardia in the WPW syndrome, the same basic prerequisite obtains as with reciprocating tachycardias of the more usual variety affecting the AV junction or complicating the WPW syndrome: unidirectional block must exist in one pathway. Under the present circumstances, this can occur in the two possible ways illustrated in Fig. 11. If the refractory period of the accessory pathway is long in the anterograde direction, all that may be required for the sinus impulse to meet this situation may be a minor increase in the heart rate (shortening of sinus cycle length) so that the sinus impulse is conducted to the ventricles slowly via the AV node, as can be seen in the fifth sinus beat in Fig. 11A. Alternatively, anterograde unidirectional block in the accessory pathway may already exist,

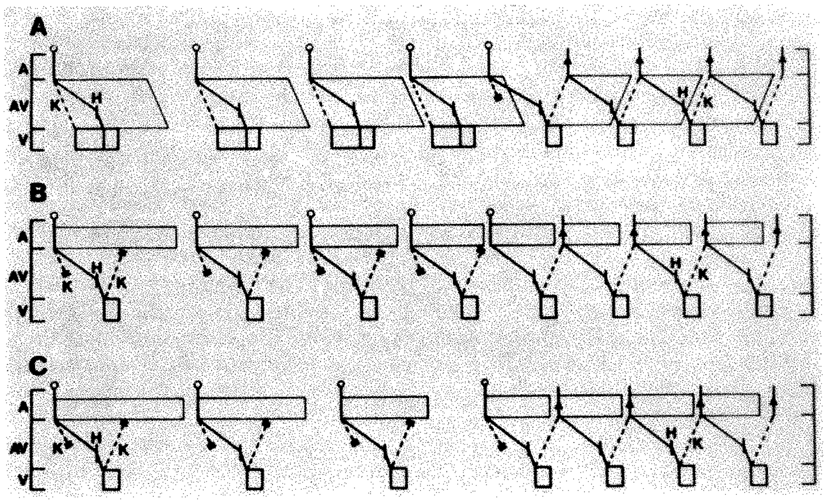

FIG. 11 *Diagrammatic representation of conduction sequences in the initiation of incessant tachycardia. A=atrium; AV=AV junction, V=ventricle; K=anomalous pathway; H=bundle of His. Impulses commencing with open circles originate in the SA node. (A) initiation of tachycardia when shortening of sinus cycle length causes an impulse traversing the anomalous pathway after the fifth beat to fall in the refractory period of the preceding sinus beat; (B) consistent anterograde block in the bypass related to the refractory period of the atrium; when the sinus cycle length and atrial refractory period shorten, retrograde bypass conduction can initiate tachycardia, as occurs with the fifth sinus beat. (C) stable sinus rate: shortening of atrial refractory period is sufficient to enable previously blocked retrograde bypass conduction to penetrate fully after the fourth sinus beat and initiate tachycardia.*

the pre-excitation being latent or concealed in the anterograde direction (Krikler, 1975) as is seen in the sinus beats in Fig. 11B. The second prerequisite follows from this: the time for conduction of the sinus beat through the AV node, when there is unidirectional block in the anomalous pathway, must be sufficiently long to permit the atrium to recover from activation by the preceding sinus beat; a possible corollary may be the need for the accessory pathway to recover from concealed anterograde conduction from the preceding sinus beat, if this had occurred.

Should these conditions be met, an atrial echo may occur when the sinus rate speeds up sufficiently for the refractory period of the anomalous pathway to be reached in the anterograde direction, this pathway now being conducted retrogradely (Fig. 11A); this may allow a burst of tachycardia to occur whenever the sinus cycle length is sufficiently short. On the other hand, when there is established unidirectional block in the anterograde pathway, speeding of the sinus rate may shorten the atrial and anomalous pathway refractory periods sufficiently to permit retrograde conduction up the anomalous pathway to the atrium, with an echo beat and tachycardia (Fig. 11B). The reciprocating AV tachycardia (whether intranodal or complicating pre-excitation) induced by exercise, in which sinus tachycardia is converted to paroxysmal tachycardia when a critical rate is reached, clearly has a similar mechanism; continuous monitoring may reveal this and exclude exercise-induced extrasystoles as the initiating factors (Krikler and Curry, 1976).

In the 3 individuals aged 18 or under, exactly similar incessant attacks of tachycardia have occurred spontaneously, or during febrile illnesses or exertion (Cases 1, 2, and 5). In Case 1, at electrophysiological study, this phenomenon was induced by the intravenous administration of isoprenaline; in Case 2 it was noted spontaneously at the start of the study but became very much more obvious after the administration of ajmaline and verapamil, and in Case 5, after ajmaline. In Case 3, incremental atrial pacing failed to initiate tachycardia until ajmaline was given, when it became incessant during the effect of the drug. Case 4 presented similar features in that, under the influence of ajmaline, which abolished anterograde bypass conduction, tachycardia was incessant; after its effect had worn off, premature stimuli were needed in order to initiate tachycardia. The classical features of incessant tachycardia were seen in Case 6 when she received vigorous antiarrhythmic therapy; the situation was not duplicated with ajmaline and verapamil during electrophysiological study.

For the electrocardiographic diagnosis of the WPW syndrome to be made in sinus rhythm, it is necessary for both the normal and anomalous pathways to function anterogradely, thus producing the characteristic fusion beat of the WPW syndrome. It is now becoming more and more obvious that in many cases there is intermittent or even permanent anterograde block in the anomalous pathway, causing the syndrome to be intermittent or indeed latent or concealed (Wilson, 1915; Slama *et al.*, 1973; Spurrell *et al.*, 1974). Unless this is appreciated, it is possible for cases of incessant junctional tachycardia to be considered to be AV nodal in origin: only Cases 3 and 4 consistently showed evidence of the WPW syndrome during sinus rhythm, it being intermittent in Cases 1, 2, and 5 (only appearing at the age of 4 in the latter even though tachycardia was present from early infancy). Case 6 never showed evidence of anterograde bypass conduction on surface electrocardiograms, electrophysiological investigation being necessary; we feel that the demonstration of an alternating cycle length during termination of the tachycardia had pointed to the presence of a bypass (Spurrell *et al.*, 1973; Curry and Krikler, 1976). As is the case in incessant AV nodal reciprocating tachycardias, cycle-length-dependent reciprocation in the WPW syndrome mainly affects younger individuals, the situation only having occurred in Case 6 on a single occasion when she received a variety of medications in rapid succession. However, there may be, as in Case 5, spontaneous improvement in the clinical condition, and the frequency and severity of the arrhythmias may wane with increasing age.

Although the mechanism may be easy to detect when it is specifically sought, the cycle length shortening may be very subtle, and perhaps impossible to affirm on conventional electrocardiograms (Fig. 6b, Case 4, and Fig. 8, Case 5) but be shown by appropriate electrophysiological studies. When there is no cycle length shortening one can only speculate that unknown factors curtail the atrial refractory period, thus permitting concealed retrograde conduction into the bypass to become manifest and establish a reciprocating circuit (Fig. 11C). This is perhaps analogous to the finding that atropine permitted re-entry to become established at an AH interval that had not provoked tachycardia before it had been given (Akhtar *et al.*, 1975); they diagnosed intranodal reciprocation but perusal of their Fig. 1, 2, and 3 suggests that their first two cases may have concealed pre-excitation.

As can be seen from our cases, the incessant mechanism may be brought to light or aggravated by antiarrhythmic agents. We have studied 5 of our patients using verapamil as an agent with predominant action on the AV node (Krikler, 1974b) and ajmaline as typical of agents that preponderantly depress myocardial (and thus bypass) conduction (Puech *et al.,* 1964). Clearly we were able to influence the respective refractory periods in such a way that the incessant situation could be achieved, on some occasions with ajmaline alone, and on others when they were given in combination. In Case 6 this effect was not achieved during study, but the incessant situation was produced by antiarrhythmic polypharmacy. We feel that in some cases of reciprocating tachycardia complicating the WPW syndrome, apparent failure to respond to therapy may reflect the fact that the agents enhance the discrepancy between the respective refractory periods of the AV node and bypass and thus enhance the opportunity for tachycardia to occur. This should be borne in mind and the patient assessed by thorough electrophysiological study before it is concluded that antiarrhythmic therapy with drugs has failed, and the patient be subjected to surgical treatment or have a pacemaker implanted. In one of our patients (Case 2) large doses of both verapamil and quinidine were required before the arrhythmias could be effectively suppressed, and we believe that remote monitoring is useful in assessing the response of such cases and enabling the pattern of initiation of arrhythmia to be seen (Coumel *et al.,* 1975).

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# 'Incessant' tachycardias in Wolff-Parkinson-White syndrome[1]

## *II: Role of atypical cycle length dependency and nodal-His escape beats in initiating reciprocating tachycardias*

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*Descriptions of patients with the Wolff-Parkinson-White (WPW) syndrome and reciprocating tachycardia in whom the initiation of the arrhythmia depended neither on the occurrence of premature beats nor on antecedent cycle-length shortening are given. In 5 the occurrence of escape beats in the bundle of His, usually in the presence of sinoatrial disease, activated the tachycardia circuit, but in the other 2 there were unusual mechanisms related to bradycardia-dependent block in the anomalous pathway, and delayed response to shortening of the atrial cycle length, respectively. Careful assessment of such mechanisms is essential for the correct choice of antiarrhythmic prophylactic therapy.*

In a previous article we have described a group of patients with the WPW syndrome in whom the induction of incessant reciprocating tachycardia depended not on extrasystoles but on critical shortening of the sinus cycle length, without antecedent PR lengthening (Krikler *et al.*, 1976a). However, not all incessant tachycardias can be explained either on this basis or because of premature beats; we have recognized 2 slightly different additional mechanisms and report 7 cases that illustrate these aspects. The methods of study have already been outlined (Krikler *et al.*, 1976a).

### Case reports

#### Case 1

A 35-year-old woman had suffered from progressively more frequent attacks of tachycardia (2 to 10 a month) for 5 years. The surface electrocardiogram showed the WPW syndrome type B (Fig. 1). Electrophysiological study, however, indicated that the accessory pathway was probably not right-sided, as endocardial mapping showed that the earliest ventricular depolarization occurred in the interventricular septum; furthermore, the induction of functional right bundle-branch block during tachycardia did not slow its rate, as it should have done had a right-sided bypass been implicated in the circuit (Slama, Coumel, and Bouvrain, 1973; Coumel and Attuel, 1974; Spurrell, Krikler, and Sowton, 1974a). Pre-excitation was suppressed by ajmaline (Fig. 1, lower panel); though two ventricular stimuli were induced in order to stop the tachycardia, the first (beat 2) would probably have sufficed as it was not followed by a retrograde P'. There was no prolongation of the PR interval in beat 10, when the tachycardia was initiated.

The onset of all bouts of tachycardia was exactly like that seen in Fig. 1, initiation being by beats identical to beat 10. As can be seen in the lower panel of Fig. 1, the first RR interval (11 to 12) is slightly longer than succeeding ones, which is against the presence of an initial common pathway. The only satisfactory explanation for the occurrence of tachycardia after beat 10 is the prolongation of the PP interval from 580 ms (beats 8 to 9) to

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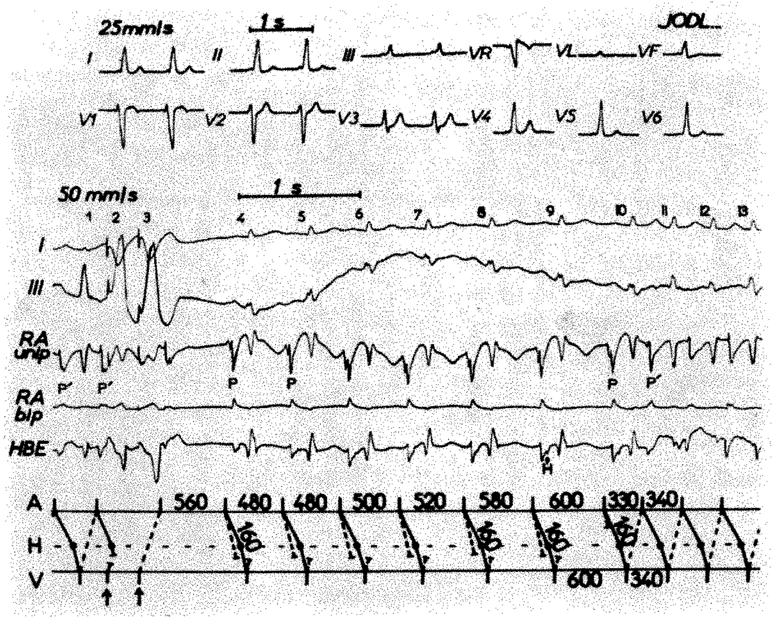

FIG. 1 *Case 1: the upper panel comprises a 12 lead electrocardiogram showing type B pre-excitation. The lower panel consists of simultaneous recordings of leads I, III, unipolar and bipolar right atrial (RA) leads, and a His bundle electrogram (HBE), with tracings taken after the administration of 50 mg ajmaline intravenously. Beat 1 is the last complex of the tachycardia, which was terminated by two ventricular stimuli (beats 2 and 3). Beats 4 to 10 are of sinus origin, all having the same, normal, PR interval (167 ms). Tachycardia is reinitiated by the lengthening of PP to 600 ms before beat 10. (In intracardiac leads P and A are used interchangeably for atrial deflections.)*

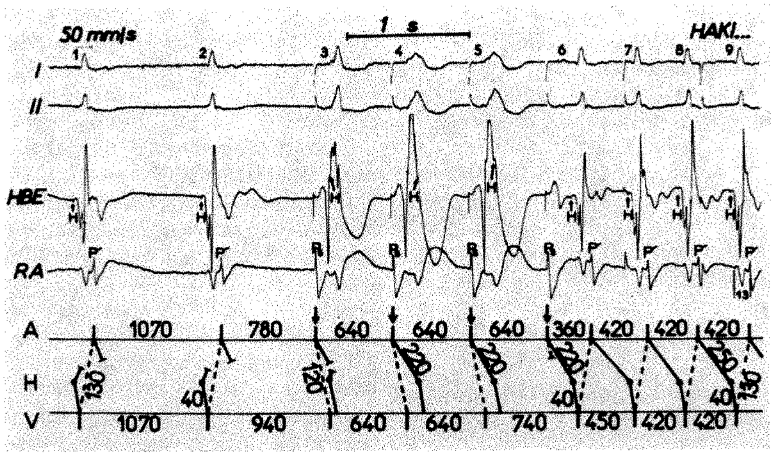

FIG. 2 *Case 2: simultaneous recording of surface leads I and II and His bundle and right atrial electrograms. Beats 1 and 2 are His bundle escape beats, at an interval of 1070 ms. Right atrial stimulation at a constant cycle length of 640 ms was started at beat 3, this beat representing fusion between the resultant atrial impulse involving the anomalous pathway and a third His bundle escape beat, H3, occurring precisely 1070 ms after H2. The fourth and fifth beats show pre-excitation with prolonged stimulus-H (Ps-H) interval of 220 ms; tachycardia is initiated by beat 6.*

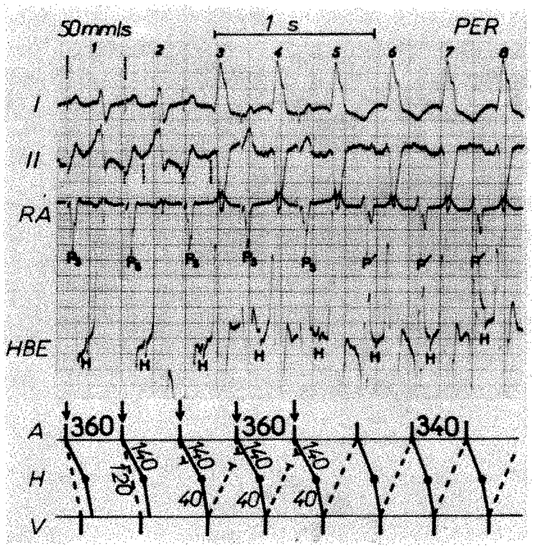

FIG. 3 *Case 3: simultaneous recordings of leads I and II, right atrial electrogram (RA) and a His bundle electrogram (HBE). The first five beats are caused by pacing at a constant rate of 167 beats a minute (stimulus-stimulus [Ps-Ps] interval 360 ms). The first two beats show clear evidence of pre-excitation, the H deflection following the beginning of QRS. The stimulus-delta (Ps-delta) interval is 120 ms, and the St-H (Ps-H) 140. In beats 1 to 5, Ps-H remains constant, and the pre-excitation pattern disappeared in beats 3, 4, and 5. Stimulation was stopped after beat 5, and re-entry at once occurred.*

600 ms (beats 9 to 10). It is assumed that concealed anterograde conduction was present within the accessory pathway in beats 4 to 9, which prevented re-entry from occurring, and that this concealed conduction had been dissipated by beat 10 because of the lengthening PP interval, a phenomenon thus most probably related to paradoxical, bradycardia-induced, block in the accessory pathway.

The phenomenon persisted for 10 minutes, as long as the ajmaline continued to be active, with spontaneous resumption of tachycardia in the identical fashion.

The tachycardia has subsequently been effectively prevented with oral amiodarone (Coumel and Bouvrain, 1973).

## Case 2

A 45-year-old man presented with frequent attacks of tachycardia, occurring especially at rest; his electrocardiogram showed the WPW syndrome type B. Electrophysiological study showed the initiation of reciprocating tachycardia following the introduction of atrial pacing at a constant slow rate (Fig. 2). Both in His bundle escape beats and in tachycardia, the retrograde conduction time up the anomalous pathway was 130 ms (beats 1, 2, 6, 7, 8, and 9). The stimulus-H (Ps-H) interval is prolonged to 220 ms in beats 4 and 5, and there is no further prolongation in beat 6 where tachycardia is initiated because of the development of anterograde block in the accessory pathway. No drugs were given during the study; the refractory period of the bypass was spontaneously long.

## Case 3

A 43-year-old man with infrequent attacks of paroxysmal tachycardia was found to have the WPW syndrome type A complicated by left bundle-branch block (Krikler *et al.*, 1976b). It was possible to initiate tachycardia by regular right atrial pacing (Fig. 3); the stage had obviously been set for re-entry at beat 3 but this was prevented by the continued pacing for another two beats. Spontaneous initiation of the tachycardia is shown in the upper panel of Fig. 4; the His bundle escape beat that followed termination of the tachycardia immediately re-established a reciprocating mechanism, as it occurred within the circuit itself. In the lower panel (Fig. 4) tachycardia started immediately after atrial stimulation had been discontinued, the His bundle escape beat after the ninth atrial stimulus immediately establishing tachycardia. Atrial driving had prevented the start of tachycardia, probably because it produced concealed anterograde conduction into the accessory pathway, thus rendering it unavailable for retrograde conduction. The His escape 2750 ms after the termination of tachycardia (Fig. 4) suggests concomitant sinoatrial disease (Mandel *et al.*, 1971).

## Case 4

A 75-year-old woman presented with alternating bradycardia and tachycardia, without overt pre-excitation before the study. Spontaneous intermittent pre-excitation occurred during the investigation (Fig. 5, upper left panel); His bundle escape beats (Fig. 5, upper right panel) do not always initiate tachycardia if for example sinus P waves, not conducted through the AV junction to the ventricles, prevent retrograde conduction from the His bundle escape beat and thus retrograde atrial activation. Validation of the location of the stimulus applied to the His bundle shown in the seventh beat in the middle panel of Fig. 5 is obtained from the HR interval of 50 ms, identical to that seen

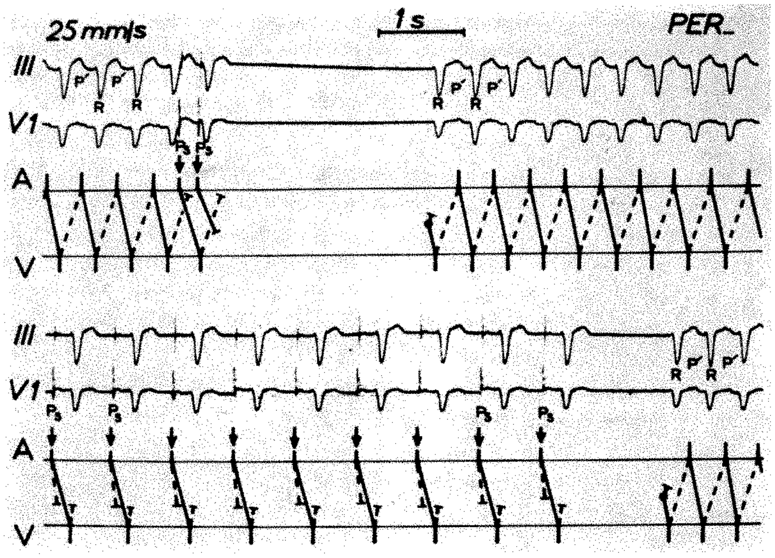

FIG. 4 *Case 3: simultaneous recordings of leads III and V1. In the upper panel, reciprocating tachycardia is apparent with retrograde P' waves; this is stopped by paired atrial stimuli (PsPs). A subsequent pause is terminated by a His bundle escape beat which reinitiates the tachycardia. In the lower panel the first nine impulses are the result of atrial stimulation at a fixed rate (Ps); the first beat after their cessation is a His bundle escape, which initiates reciprocating tachycardia.*

in the spontaneous sinus beat and the His bundle escape beat in the bottom panel in this figure. In this patient pre-excitation was always latent, except briefly during this study, being represented only in the limb leads, so the praecordial pattern is not known. Because the stimulus was applied high in the right atrium, the Ps-R and Ps-delta intervals are longer than during low right atrial stimulation (middle panel).

## Case 5

A 60-year-old woman with a history of alternating attacks of tachycardia and bradycardia had been considered to have reciprocating AV nodal tachycardia. The first run of tachycardia (Fig. 6) showed alternating cycle lengths. Apparent sinus bradycardia may in reality reflect 2:1 sinoatrial block; so the apparently premature His bundle beat, which would have been early in relation to sinus bradycardia, could reflect a genuine escape beat in relation to sinoatrial block. One might be tempted to diagnose reciprocating AV nodal tachycardia, but the alternating cycle lengths suggested an extranodal bypass (Spurrell, Krikler, and Sowton, 1974b; Curry and Krikler, 1976), and the fact that the tachycardia was slower in the presence of left bundle-branch block than during its absence (171 as opposed to 182 beats a minute) pointed to the presence of an otherwise concealed left-sided anomalous pathway (Slama *et al.*, 1973; Spurrell *et al.*, 1974a).

## Case 6

A 68-year-old woman had suffered from progressively more troublesome tachycardia for 25 years, and was found to have the WPW syndrome type A (Fig. 7) complicated by left bundle-branch block (Krikler *et al.*, 1976b) and sinoatrial disease; in tachycardia the QRS complexes show an LBBB pattern (Fig. 8). She showed initiation of tachycardia by two mechanisms; (a) with progressively faster right atrial pacing (Fig. 7); and (b) following His bundle escapes, provided that their retrograde conduction up the anaomalous pathway was not blocked by sinus impulses (Fig. 8), analogous to the situation seen in Case 4 (Fig. 5). Continued atrial stimulation prevented further attacks during the study by suppressing the occurrence of escape beats.

## Case 7

A 67-year-old man had suffered from recurrent supraventricular tachycardia for more than 50 years; numerous electrocardiograms had all failed to show pre-excitation except transiently im-

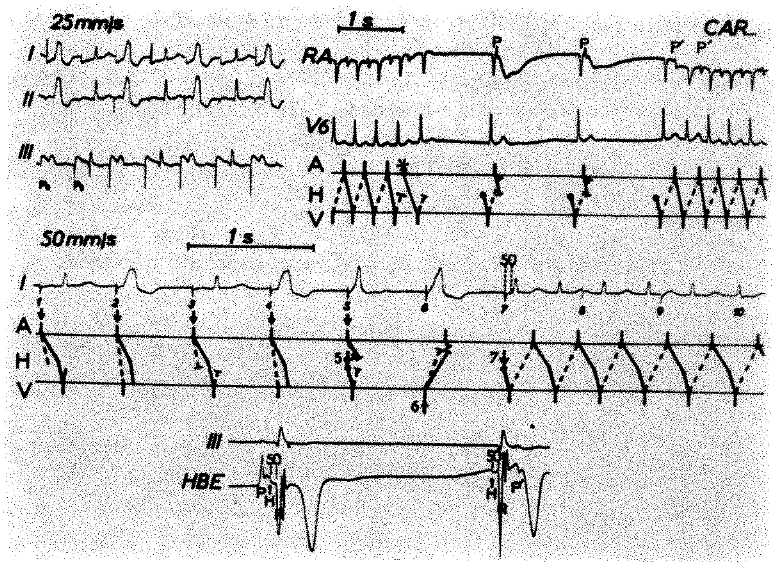

FIG. 5 *Case 4: the upper two panels were recorded at a paper speed of 25 mm/s, the middle and bottom at 50 mm/s. Left upper panel shows the three standard leads recorded simultaneously, with regular right atrial pacing: alternating pre-excitation is seen. In the right upper panel a right atrial electrogram is shown simultaneously with V6: the first five QRS complexes represent reciprocating tachycardia, which is terminated by a spontaneous atrial premature beat (*); the three beats thereafter reflect escape in the His bundle, the third one restarting the reciprocating tachycardia.*

*Middle panel: the first four stimuli were applied low in the right atrium and the QRS complexes show alternating pre-excitation; the fifth stimulus produces a fusion beat caused by activation of atrium and His bundle and probably the uppermost part of the interventricular septum. The sixth stimulus was applied to the interventricular septum, and the seventh to the bundle of His, with a Ps-R interval of 50 ms; this resulted in the initiation of the tachycardia (the eighth, ninth, and tenth stimuli were ineffective). Only the seventh stimulus triggered tachycardia because it was the only one in which the His bundle alone was stimulated, without any atrial or ventricular activation.*

*Bottom panel shows simultaneous recordings of leads III and HBE: the first complex is a spontaneous sinus beat and the second a His bundle escape beat. Note that in each case the HR interval is 50 ms.*

mediately after conversion to sinus rhythm by verapamil (Krikler and Curry, 1976). Electrophysiological study confirmed the presence of type A pre-excitation (Fig. 9A); the bypass refractory period in the anterograde direction was 230 ms. In Fig. 9B, after he had received intravenous ajmaline (0·75 mg/kg body weight), each termination of tachycardia by induced single ventricular premature beats was followed by a His bundle escape beat which invariably reinitiated the tachycardia.

## Discussion

It is generally agreed that three conditions are necessary for the establishment of a re-entry tachycardia: (a) the existence of a potential circuit; (b) unidirectional block in the circuit; (c) slowing of conduction so that the travelling impulse does not encounter a refractory area at any point during its circuit. Even if the first prerequisite is present, the latter two are often obscured at the initiation of a paroxysm though in reality one or other may be present, albeit potentially rather than overtly. In the previous article we have shown that, for example, in the WPW syndrome, slowing of conduction (requirement (c)) need not implicate the anterograde pathway; there was no lengthening of the PR interval at the start of the tachycardia (Krikler *et al.*, 1976a). The initiation of the paroxysm was linked to the development of unidirectional block in the accessory pathway, perhaps seen only as the disappearance of concealed anterograde conduction along that route.

A variety of these aspects is illustrated in the 7 cases now presented. *Block in the accessory pathway*, however produced, led to tachycardia in all our cases; this had been produced pharmacologically (Case 7); by phase 3 block caused by an increase in the rate of the stimulation (Case 6); or by phase 3 block undoubtedly the result of a fatigue phenomenon, the rate of stimulation not having been increased (Cases 2 and 3). The situation in Case 1 was highly unusual, in that the block was paradoxical, because of prolongation of the atrial cycle length, in association with concealed as opposed to overt anterograde conduction in the accessory pathway.

*Lengthening of the PR (or AH) interval* at the start of tachycardia has been extensively discussed

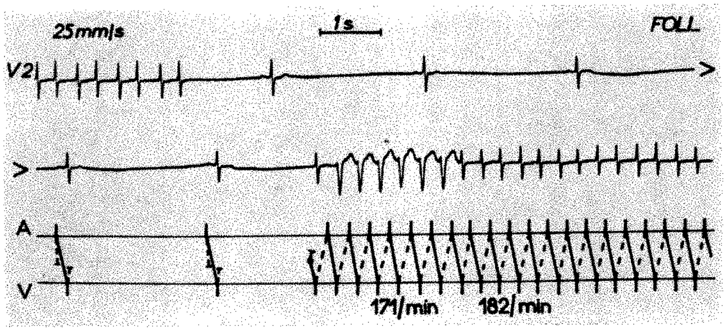

FIG. 6 *Case 5: continuous tracing of V2 (the ladder diagram refers to the bottom strip). In the upper panel, tachycardia is present at the start of the tracing, with alternating cycle lengths; after spontaneous cessation, sinus bradycardia is noted for five beats, followed by a premature His bundle beat that restarted the tachycardia. The first six beats of tachycardia showed left bundle-branch block, with a heart rate of 171 beats a minute; this was followed by normalized conduction at a rate of 182 beats a minute.*

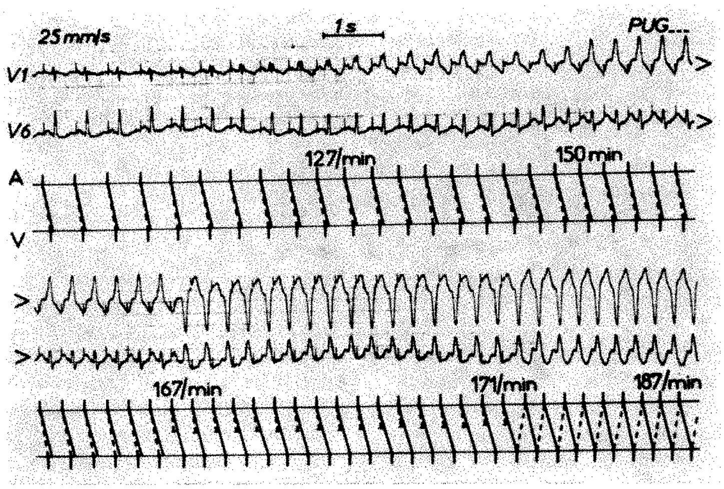

FIG. 7 *Case 6: continuous simultaneous tracings of leads V1 and V6, showing the effects of gradually increasing right atrial pacing. There is no good evidence of pre-excitation at slow pacing rates, but this becomes increasingly evident as the pacing rate exceeds 120 beats a minute. At a pacing rate of 167 beats a minute anterograde bypass block is induced; at 171 beats a minute, when pacing was stopped, reciprocating tachycardia showing a left bundle-branch block pattern was established at a rate of 187.*

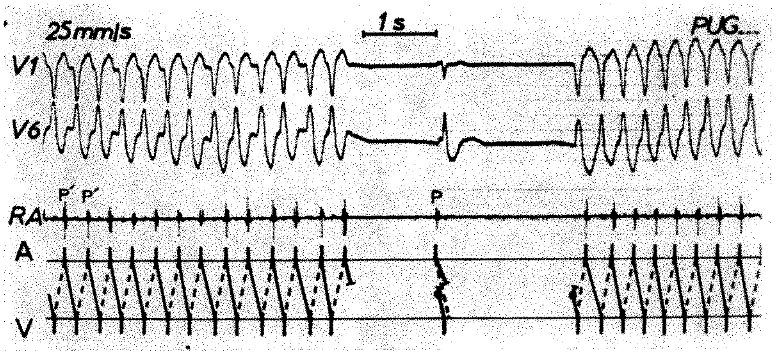

FIG. 8 *Case 6: leads V1, V6, and RA, showing spontaneous cessation of tachycardia with LBBB pattern; the subsequent beat reflects fusion between a sinus impulse with anterograde bypass conduction, and a His bundle escape; the following beat is a His bundle escape that reinitiates tachycardia.*

(Goldreyer and Damato, 1971; Rosen, 1973), but the precise importance of this phenomenon needs to be reassessed. It need not be present (Case 1), as we have also shown in the preceding paper (Krikler *et al.*, 1976a). Even if PR prolongation is present, as in Cases 2, 3, and 6, tachycardia started without additional prolongation, the accessory pathway being blocked in Case 2; the onset was seen in Cases 3 and 6 when atrial stimulation was interrupted. In addition, these latter two cases show that PR lengthening is by no means essential, since the tachycardia could be initiated by His bundle escape beats, without prolongation of the conduction time.

*Escape beats within the re-entry circuit* constitute an important mechanism for the initiation of attacks (Cases 3, 5, and 7), but this still conforms with the requirements for re-entry mentioned above. Thus, in Case 2 the escape beats failed to provoke tachycardia in the presence of concealed retrograde conduction into the normal pathways; similarly, as in Cases 4 and 6, concealed anterograde conduction of the P waves also prevented the onset of tachycardia. On the other hand, lack of atrial activation, as indicated by the absence of a P wave, could enable an incessant tachycardia to start (Case 7). We have been able to show the presence of the WPW syndrome in these cases, but this does not mean that this phenomenon cannot occur in nodal re-entry; it does however appear to us much less likely because under those circumstances the escape occurs *outside* the circuit.

Thus, while in patients with reciprocating tachycardias associated with pre-excitation, attacks are usually initiated by extrasystoles (Durrer *et al.*, 1967) or sometimes by shortening of the sinus cycle length (Krikler *et al.*, 1976a), a different group of mechanisms can be shown to be of importance. That nodal-His bundle escape beats, originating as they do within the substrate for the circuit, are able to induce tachycardias with ease is evident in 5 of our patients, often in the context of sinoatrial disease, itself an important mechanism for the occurrence of paroxysmal tachycardia. This has indeed been recognized in the Wolff-Parkinson-White syndrome complicated by atrial fibrillation (Dreifus, Kimbiris, and Wellens, 1973) and reciprocating AV tachycardia (Harper *et al.*, 1974). Sinoatrial disease was present or considered highly likely in three of our patients (Cases 3, 5, and 6) but His bundle escape beats also occurred when it was not possible to affirm its presence (Cases 4 and 7); in Case 7 the escapes were associated with the administration of ajmaline. It is self-evident that for tachycardia to occur, His bundle escape beats must be conducted, anterogradely better than retrogradely, thus leaving the AV node ready for the circus wave once it has reached the atrium via the bypass.

These phenomena are of interest in that they may explain the occurrence of tachycardias complicating pre-excitation in the absence of premature beats, and without immediately antecedent conduction delay in the blocked pathway. Nodal-His escape beats are potentially of great importance but other mechanisms are more complex and each atypical case needs the most careful scrutiny in order to define possible causes for tachycardia. That this is of therapeutic as well as of academic significance is shown by Case 6, in whom drug therapy proved unhelpful by producing further depression of the SA node, leading to syncope, as well as a consequent increased tendency to tachycardia induced

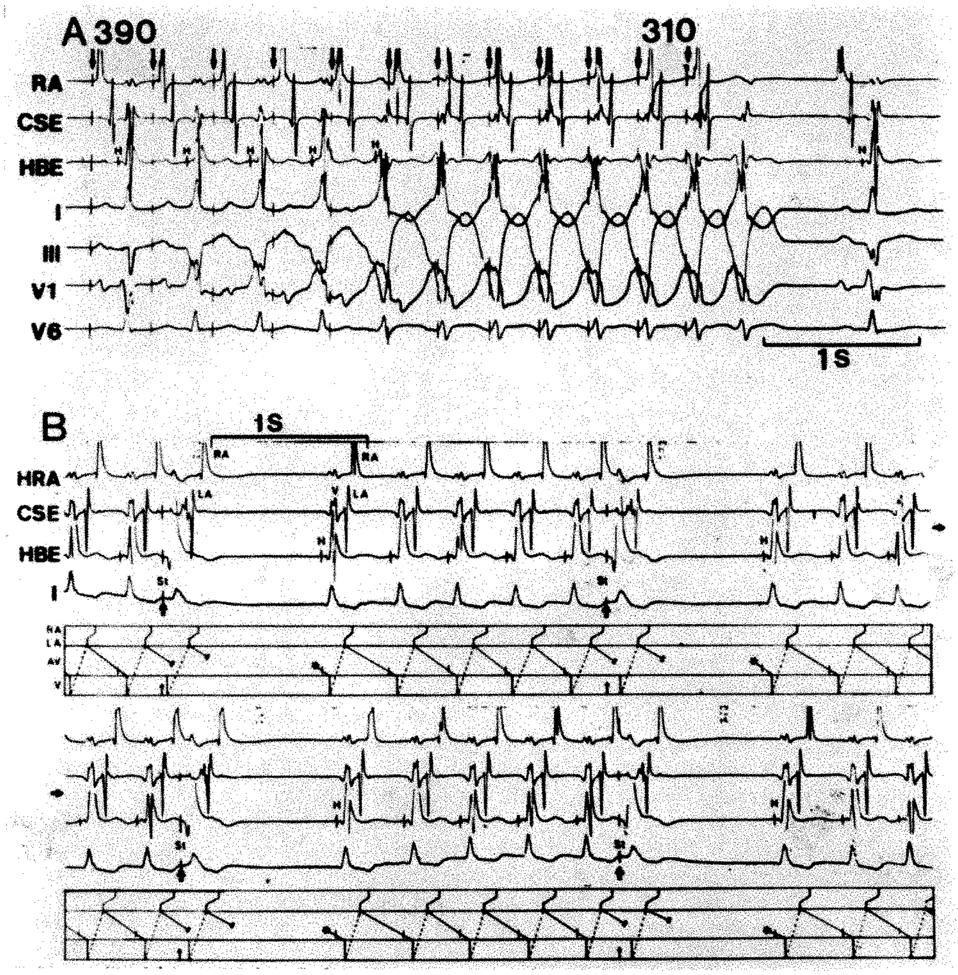

FIG. 9 *Case 7: (A) RA, coronary sinus electrogram (CSE), HBE, and leads I, III, V1, and V6 bringing out the pre-excitation as the pacing rate was progressively increased (intervals between stimuli decreased from 390 to 330 ms). (B) Continuous tracings (HRA, CSE, HBE, and lead I), showing termination of tachycardia by ventricular stimuli (St) and immediate reinitiation by His bundle escape beats.*

by the junctional escape beats (Krikler *et al.*, 1976b). That more than one mechanism may apply in a patient is well shown by the same case, who had tachycardia initiated both by progressive atrial pacing and by the junctional escape beats.

While these atypical types of tachycardia are unusual, they are by no means rare, and may apply particularly to older subjects in whom the junctional escape beats, perhaps originating in the bundle of His, occur more frequently as a consequence of disease affecting proximal physiological pacemaking cells, e.g. sinoatrial disease. Successful therapy, both for the attacks themselves and for their prophylaxis, thus requires careful understanding of these mechanisms, the nature of which should be defined in all patients who present with apparently atypical onset of tachycardia. It is important to remember that depressant antiarrhythmic drugs may paradoxically induce incessant tachycardias in this way; elucidation of apparent paradoxical response of this sort may be of practical importance as well as indicating the reason for the apparent failure of treatment. Finally, it is in cases like this that long-term pacing may be particularly helpful in the prevention of attacks, an aspect that we are currently exploring.

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# Coronary artery disease in patients dying from cardiogenic shock or congestive heart failure in the setting of acute myocardial infarction

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*Pathological findings in the heart and particularly in the coronary arteries are reported from 70 patients dying from pump failure after acute myocardial infarction. Fifty of the patients had died in cardiogenic shock, the remainder from refractory congestive heart failure.*

*Three-vessel disease (≥75% occlusion) was present in 68 per cent of the group with cardiogenic shock but in only 35 per cent of those with fatal congestive heart failure ($P<0.02$). In both groups there was an almost equal incidence (84% for cardiogenic shock and 80% for congestive heart failure) of severe disease (≥75% occlusion) over a long segment of the left anterior descending artery.*

*However, there were differences between the two groups regarding the involvement of the other coronary arteries. Whereas patients with cardiogenic shock generally showed severe disease over a long segment in all coronary arteries, in 60 per cent of those with congestive heart failure there was only local severe narrowing of the right coronary artery with little or no narrowing of the peripheral part. Similarly, 60 per cent of those with congestive heart failure had less than 75 per cent narrowing in the left circumflex artery. These anatomical findings may be of relevance with regard to desirability of acute coronary bypass surgery in patients with pump failure after acute myocardial infarction.*

At present pump failure is the most important cause of hospital mortality in patients with acute myocardial infarction. Medical treatment of severe pump failure is often unsuccessful because of the presence of extensive myocardial damage (Harnarayan *et al.*, 1970; Page *et al.*, 1971; Alonso *et al.*, 1973). Fatal pump failure after acute myocardial infarction occurs in two distinct clinical syndromes, namely cardiogenic shock and refractory congestive heart failure. Most patients die from cardiogenic shock, but some, without developing the clinical picture of cardiogenic shock, die from persistent refractory congestive heart failure. In order to treat these syndromes, several investigators have advocated use of circulatory assistance (such as intra-aortic balloon counterpulsation) followed by coronary bypass surgery (Dunkman *et al.*, 1972; Scheidt *et al.*, 1973; Miller *et al.*, 1974; O'Rourke *et al.*, 1975; Willerson *et al.*, 1975). However, the efficacy of these procedures remains controversial (Cohen, 1974; Kuhn, 1974). It seemed to us that the success or failure of these measures could well relate to the underlying cardiac pathology. We have, therefore, studied the hearts of 70 patients who died either from cardiogenic shock or refractory congestive heart failure in the setting of acute myocardial infarction, paying particular attention to the state of the coronary arteries.

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## Subjects and methods

The material studied was derived from a group of 1050 patients consecutively admitted with acute myocardial infarction. Table 1 shows age, sex distribution, localization, and number of infarctions in patients who died from cardiogenic shock, congestive heart failure, necropsied and not necropsied, and other causes, and those who survived. Patients who died either from cardiogenic shock or other causes had a higher mean age ($P<0.05$) than those who survived. Patients who died from cardiogenic shock and congestive heart failure had a higher incidence of both previous infarction ($P<0.01$) and

TABLE 1 *Sex, age, number, and site of infarction in patients who died from cardiogenic shock, congestive heart failure, or other causes and in those who survived*

| | *No.* | *Sex ratio* | | | *Mean age* | | *No. of infarction* | | | *Site of infarction* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *M* | *F* | *P value vs surv.* | *(y ± SD)* | *P value vs surv.* | *First* | *Recurr.* | *P value vs surv.* | *AS* | *Other sites* | *P value vs surv.* |
| CS (all cases) | 83 | 56 | 27 | NS | 68·0 ± 9·1 | <0·05 | 54 | 29 | <0·01 | 41 | 42 | <0·01 |
| CS (necropsied cases) | 50 | 36 | 14 | NS | 68·6 ± 8·3 | <0·05 | 29 | 21 | <0·01 | 24 | 26 | <0·01 |
| CHF (all cases) | 31 | 27 | 4 | NS | 64·7 ± 10·3 | NS | 15 | 16 | <0·01 | 18 | 13 | <0·01 |
| CHF (necropsied cases) | 20 | 17 | 3 | NS | 67·2 ± 9·8 | NS | 12 | 8 | <0·05 | 13 | 7 | <0·01 |
| Other causes of death | 70 | 47 | 23 | NS | 69·7 ± 9·8 | <0·05 | 57 | 13 | NS | 30 | 40 | <0·01 |
| Survivors | 866 | 635 | 231 | | 63·0 ± 10·2 | | 678 | 188 | | 158 | 708 | |

Abbreviations: AS=anteroseptal; CHF=congestive heart failure; CS=cardiogenic shock.

a higher incidence of anteroseptal infarction ($P<0\cdot01$) than those who survived.

One hundred and fourteen patients died from pump failure. Of these, 70 patients had necropsies and the hearts from these patients form the basis of this report. Fifty of these patients died of cardiogenic shock, while the 20 remaining patients died from refractory congestive failure.

Cardiogenic shock was defined according to Killip's (Wolk, Scheidt, and Killip, 1972) classification type IV: i.e. blood pressure under 90 mmHg (12·0 kPa), a decreased urine production of less than 20 ml per hour, and signs of reduced peripheral circulation.

The group of patients with refractory congestive heart failure died in circumstances covered in Killip's classification by group II and III, i.e. persistent râles over both lung fields, with urine production maintained largely above 20 ml per hour.

The diagnosis of acute myocardial infarction was based on a typical history of chest pain correlated with the appearance of diagnostic Q waves and characteristic serial changes in serum enzymes.

Excluded from this study were all patients who died from pump failure secondary to ruptured papillary muscles or a ruptured ventricular septum, together with those with primary arrhythmias. In 52 of the 70 cases postmortem coronary angiograms were made. The right and left coronary arteries were selectively filled with a barium gelatin mixture at a pressure of approximately 40 mmHg (5·3 kPa). In addition, in each heart the coronary arteries were studied by serial sectioning at 3 to 5 mm intervals. Each section was inspected and the degree of luminal narrowing was determined, usually as a percentage of the external diameter. The observed pathology was reconstructed on drawings of the coronary arteries. Only obstructive lesions with more than a 75 per cent luminal narrowing were used for classification of coronary disease. A lesion was considered to be 'local' when only a single obstructive lesion was present, extending over a segment of 5 mm or less. Multiple obstructions or those extending over a segment longer than 5 mm were considered as 'diffuse' lesions. If possible (see under results) the size of the infarct was estimated grossly by inspection of the myocardium. When deemed necessary these findings were supplemented by microscopical studies. The significance of differences was analysed by use of the $\chi^2$ test. The significance of difference in mean values was tested by the Student's t test.

## Results

Age, sex, site, and number of infarcts for the 70 patients studied are shown in Table 1.

In terms of the onset of symptoms and moment of death, cardiogenic shock and refractory congestive heart failure constitute two clinically distinguishable groups (Fig. 1). Cardiogenic shock developed within 24 hours of onset of symptoms of acute myocardial infarction in 42 of 50 patients (84%). In contrast, fatal congestive heart failure developed over a 3-week period after onset of acute myocardial infarction ($P<0\cdot01$). Eighty-six per cent of patients with fatal cardiogenic shock died within 24 hours of its onset and 98 per cent died within 3 days. In contrast, only 20 per cent of patients with fatal congestive heart failure died within 24 hours ($P<0\cdot01$), 25 per cent ($P<0\cdot01$) dying within 3 days of the onset of symptoms (Fig. 2).

### Size of infarction

Determination of the size of the myocardial infarct was hampered in those patients dying within 24 hours of onset of infarction since the extent of the infarct could not be determined with certainty. For this reason, in only 28 cases (11 patients with cardiogenic shock and 17 patients with congestive

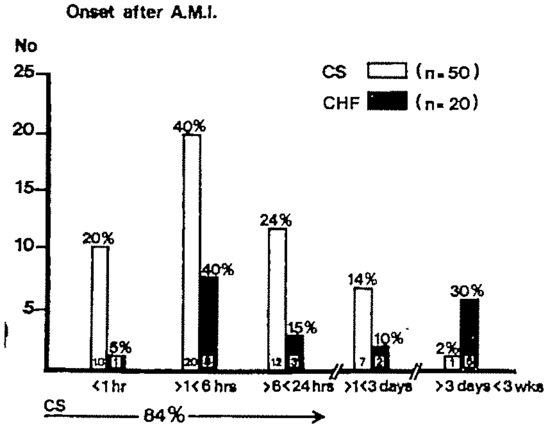

FIG. 1 *Time of onset of cardiogenic shock (CS) after first symptoms of acute myocardial infarction (AMI) as compared with the time of onset of lethal congestive heart failure (CHF).*

heart failure) was it possible to analyse infarct size. No major difference in size of infarcted myocardium was found between the group with cardiogenic shock and that with congestive heart failure. In both groups a 40 to 50 per cent involvement of left ventricular myocardium was present. The papillary muscles were involved in the infarction in 5 hearts from patients dying with congestive heart failure.

## Coronary artery pathology

Severe atherosclerotic involvement of the coronary arteries was present in hearts obtained both from patients with cardiogenic shock and from those dying with refractory congestive heart failure (Table 2).

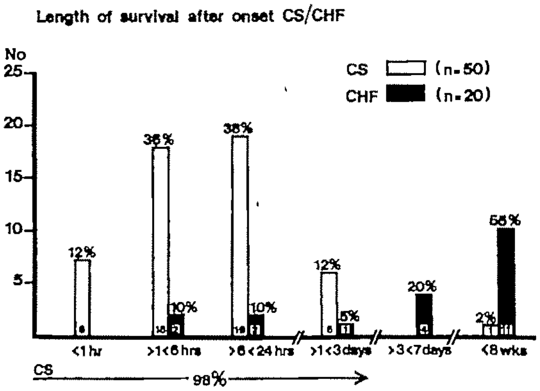

FIG. 2 *Length of survival after onset of cardiogenic shock (CS) and lethal congestive heart failure (CHF).*

TABLE 2 *One, two, or three-vessel coronary artery disease* in patients dying from cardiogenic shock (N=50) and in those dying from congestive heart failure (N=20)*

| *CAD* | *One* *No.* | % | *Two* *No.* | % | *Three* *No.* | % |
|---|---|---|---|---|---|---|
| CS | 0 | | 16 | 32 | 34 | 68 |
| CHF | 4 | 20 | 9 | 45 | 7 | 35 |

Abbreviations: CAD=coronary artery disease; CHF=congestive heart failure; CS=cardiogenic shock.
*Luminal narrowing of ≥75 per cent.

The left anterior descending coronary artery was always diseased. Usually, this artery was heavily calcified and exhibited severe stenosis of a diffuse type, often complicated by total occlusion. The two clinical groups showed no differences regarding the degree and extent of involvement of the anterior descending artery. However, striking differences between the two clinical groups were noted with regard to the severity and extent of sclerotic disease in the other arteries. In patients with congestive heart failure the left circumflex artery and the right coronary artery were less involved than in patients with cardiogenic shock (Table 3).

Obstructive lesions in the right coronary artery and the left main stem in patients with congestive heart failure were mostly of a localized type (<5 mm) and were confined to the proximal parts of the arteries. Patients with cardiogenic shock, in

TABLE 3 *Severity of luminal narrowing of coronary arteries in patients dying from cardiogenic shock (N=50) and congestive heart failure (N=20)*

| | | *Luminal narrowing* *<75%* *No.* | % | *≥75%* *No.* | % | *P value* *CS vs CHF* |
|---|---|---|---|---|---|---|
| RCA | CS | 4 | 8 | 46 | 92 | <0·01 |
| | CHF | 6 | 30 | 14 | 70 | |
| LMS | CS | 31 | 62 | 19 | 38 | NS |
| | CHF | 16 | 80 | 4 | 20 | |
| LAD | CS | 0 | | 50 | 100 | NS |
| | CHF | 0 | | 20 | 100 | |
| LCA | CS | 13 | 26 | 37 | 74 | <0 01 |
| | CHF | 12 | 60 | 8 | 40 | |

Abbreviations: CHF=congestive heart failure; CS=cardiogenic shock; LAD=left anterior descending artery; LCA=left circumflex artery; LMS=left main stem; RCA=right coronary artery.

TABLE 4 *Length of segment involved in coronary artery disease* in patients dying from cardiogenic shock (N=50) and in those dying from congestive heart failure (N=20)*

| | | *<5 mm* | | *>5 mm* | | *P value* |
|---|---|---|---|---|---|---|
| | | *No.* | *%* | *No.* | *%* | *CS vs CHF* |
| RCA | CS | 11 | 22 | 35 | 70 | <0·01 |
| | CHF | 12 | 60 | 2 | 10 | |
| LMS | CS | 3 | 6 | 16 | 32 | <0·01 |
| | CHF | 4 | 20 | 0 | | |
| LAD | CS | 8 | 16 | 42 | 84 | NS |
| | CHF | 4 | 20 | 16 | 80 | |
| LCA | CS | 16 | 32 | 21 | 42 | NS |
| | CHF | 5 | 25 | 3 | 15 | |

Abbreviations: CHF=congestive heart failure; CS=cardiogenic shock; LAD=left anterior descending artery; LCA=left circumflex artery; LMS=left main stem; RCA=right coronary artery.

*Luminal narrowing of $\geqslant 75$ per cent.

contrast, had atherosclerotic changes of diffuse type in both these arteries (Table 4). Three-vessel disease was present in 68 per cent of the patients dying from cardiogenic shock, but in only 35 per cent of the patients dying from congestive heart failure ($P < 0{\cdot}02$). One-vessel disease was present in 20 per cent of patients with congestive heart failure, but did not occur at all in patients with cardiogenic shock (Table 2).

It was not possible to identify differences in either severity or extent of coronary artery pathology between patients with 'early' cardiogenic shock (i.e. onset within 24 hours of acute myocardial infarction) and those dying from 'late' cardiogenic shock (i.e. onset of shock later than 24 hours of acute myocardial infarction).

## Discussion

For the most part, our data endorse the well-known fact that patients who die from pump failure in the setting of acute myocardial infarction have extensive loss of myocardium and severe coronary artery disease (Bolooki *et al.*, 1971; Alonso *et al.*, 1973; Scheidt *et al.*, 1973; Buja and Roberts, 1974; Willerson *et al.*, 1975). However, our study additionally shows that important differences exist with regard to localization and extent of coronary artery disease between patients dying in cardiogenic shock and those dying in congestive heart failure. To the best of our knowledge, this finding has not been stressed previously. Both groups of patients had similar severe involvement of the left anterior descending coronary artery. In the majority of patients who died of refractory congestive heart failure (60%), there was minor involvement of the right coronary artery, representing only a localized narrowing with little or no distal involvement. In patients who died from cardiogenic shock there was severe diffuse involvement of this artery. These differences in extent of coronary artery disease were also noted between the two groups with regard to the left circumflex artery.

It is possible that these anatomical findings may have therapeutic implications. In recent years more aggesssive approaches have been advocated in the treatment of the patient with severe pump failure complicating acute myocardial infarction (Dunkman *et al.*, 1972; Scheidt *et al.*, 1973; Miller *et al.*, 1974; O'Rourke *et al.*, 1975). It has been suggested that circulatory assist should be initiated followed by acute bypass surgery. Differences in reported results undoubtedly relate primarily to the extent of the myocardial damage. Our findings are in accordance with those described by Harnarayan *et al.* (1970), in that the extent of the infarction is similar in both patients dying from congestive heart failure and from cardiogenic shock. An explanation for the differences in clinical course, in the setting of a similar infarct size, could be that in these patients with congestive heart failure after their primary myocardial infarct, a gradual extension of the infarcted area leads to fatal congestive heart failure.

Our findings suggest that, because of the differences in coronary artery involvement, early coronary bypass surgery is far more likely to be of benefit in patients with refractory congestive heart failure than in patients with cardiogenic shock. The early recognition of the group of patients with pump failure presenting as refractory congestive failure therefore becomes of crucial importance. The problem remains as to how these patients are to be detected in the immediate postinfarction period. Our study revealed that patients who developed congestive heart failure did so over a long period of time, with no initial clinical signs which might have indicated the fatal outcome. They differed completely from patients with cardiogenic shock who for the most part developed their complication within 24 hours of the acute infarction. They also generally died within a few days. In an attempt to determine the profile of those patients with congestive heart failure who are at high risk, we noted that 77 per cent of patients dying from failure had either an anteroseptal infarction or a recurrent infarction. The prognostic significance of these factors has been reported previously (Lie *et al.*, 1974, 1975). In addition, the outcome for these patients is largely determined by whether or not they respond to medical treatment. If they do not respond, refractory congestive heart failure in the setting of an acute myocardial infarct is a bad prognostic sign. Our findings, therefore, stress the necessity for careful study of the group of patients who develop refractory congestive heart failure after acute infarction in order to identify that subgroup of patients in which the outcome will be fatal.

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# Diagnosis of endocardial cushion defect with cross-sectional and M-mode scanning echocardiography

## *Differentiation from secundum atrial septal defect*[1]

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*Twelve cases of endocardial cushion defect were studied before and after operation with ultrasono-cardiotomography (tomography) (cross-sectional echocardiography, two-dimensional echocardiography, B-scan echocardiography) and M-mode scan along a horizontal section of the heart. For comparison, 20 healthy subjects, 18 cases of mitral valvular disease, 4 cases of congestive cardiomyopathy, 1 case of partial anomalous pulmonary venous drainage, and 25 cases of atrial septal defect of secundum type were also examined with the same technique.*

*In cases without cardiac malformation, the echo of the anterior mitral valve was usually continuous medially with that of the interatrial septum in the horizontal plane at the level of the membranous septum. This feature was clearly recorded in all cases with right heart enlargement.*

*In ostium secundum atrial septal defect the echo of the anterior mitral valve continued into that of the interatrial septum. An echo interruption was shown, indicating the defect itself to be in the middle part of the interatrial septum.*

*In all the cases of endocardial cushion defect which we examined, discontinuity was shown between the echo of the anterior mitral valve and that of the interatrial septum. This discontinuity was interpreted as indicating the defect itself. The mitral valve ring echo was close to the basal end of that of the interventricular septum, possibly reflecting an abnormal attachment of the mitral valve. In all cases, after operation, the echo of the artificial interatrial septum was recorded, continuous with that of the anterior mitral valve.*

*The features of the echocardiographic sweep from the anterior mitral valve to the interatrial septum were thus different in the three groups. These echocardiographic differences are thought to correspond to the anatomical differences between the normal, atrial septal defect of secundum type, and endocardial cushion defect, and are essential features differentiating them from each other.*

At present, the diagnosis of endocardial cushion defect is based on haemodynamic and angiographic studies (Baron *et al.*, 1964). Conventional non-invasive examinations such as chest *x*-ray films, phonocardiography, and electrocardiography, help towards a diagnosis of this malformation. Incomplete right bundle-branch block with left axis deviation in the electrocardiogram is one of the characteristic features (Burchell, DuShane, and Brandenburg, 1960). However, this is not always found in this malformation (Toscano-Barbosa, Brandenburg, and Burchell, 1956) and occasionally it is seen in cases of atrial septal defect of secundum type (Harrison and Morrow, 1963). Therefore, to differentiate endocardial cushion defect from other cardiac malformations, including atrial septal defect of secundum type, a further non-invasive technique is needed.

Recently, echocardiography has been widely used

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in clinical cardiology, because it has the advantage of being non-invasive with no discomfort to the patient. It has been proved to be a useful aid in the diagnosis of congenital heart disease (Chung *et al.*, 1973; Dillon *et al.*, 1973; Gramiak *et al.*, 1973; Lundström, 1973; Meyer and Kaplan, 1972; Nimura *et al.*, 1974; Popp *et al.*, 1974). In endocardial cushion defect, several characteristic patterns in standard echocardiograms have been reported (Gramiak *et al.*, 1972; Pieroni, Homcy, and Freedom, 1975; Williams and Rudd, 1974).

Ultrasono - cardio - tomography (tomography) (cross-sectional echocardiography, two-dimensional echocardiography, B-scan echocardiography) allows the relations between intracardiac structures to be seen, because it corresponds precisely to the anatomy of the heart (Ebina *et al.*, 1967; King, 1973; King, Steeg, and Ellis, 1973; Nimura *et al.*, 1971, 1974; Matsumoto, 1973; Matsumoto *et al.*, 1975; Tanaka *et al.*, 1971). Sahn *et al.* (1974) attempted to diagnose endocardial cushion defect by means of two-dimensional echocardiography with multi-crystal scan; however, they could not detect the defect itself but only the abnormalities of the echo of the mitral apparatus.

As previously reported by Nimura *et al.* (1971), Matsumoto (1973), and Matsumoto *et al.* (1975), tomographic visualization of the defect of the interatrial septum was obtainable in patients with ostium secundum atrial septal defect. This study was aimed at examining the anatomical abnormalities associated with endocardial cushion defect by ultrasono-cardio-tomography and M-mode scan. In combination, these two techniques were able to detect the interatrial septal defect and the abnormal attachment of the anterior mitral valve. The different site of the atrial septal defect in endocardial cushion defect compared with that in atrial septal defect of secundum type was clearly recognized by tomographic visualization.

## Subjects and methods

A commercially available ultrasonograph, an Aloka SSD-30B, was used with a 2·25 MHz, 10 mm-diameter transducer with a pulse repetition rate of 1500 Hz. This equipment allowed us to record both standard and cross-sectional echocardiographic recordings by switching modes of display. To obtain the tomogram, the transducer was attached to the end of a guide arm giving reference to its position and angle (Fig. 1). The echoes at multiple points were recorded by slow manual scanning. The equipment was connected to a device, an Aloka SCU-1F, which had delay and gate circuits triggered by the electrocardiogram. The duration of the display time was set at 30 milliseconds by the gate circuit, and the onset of this display time was

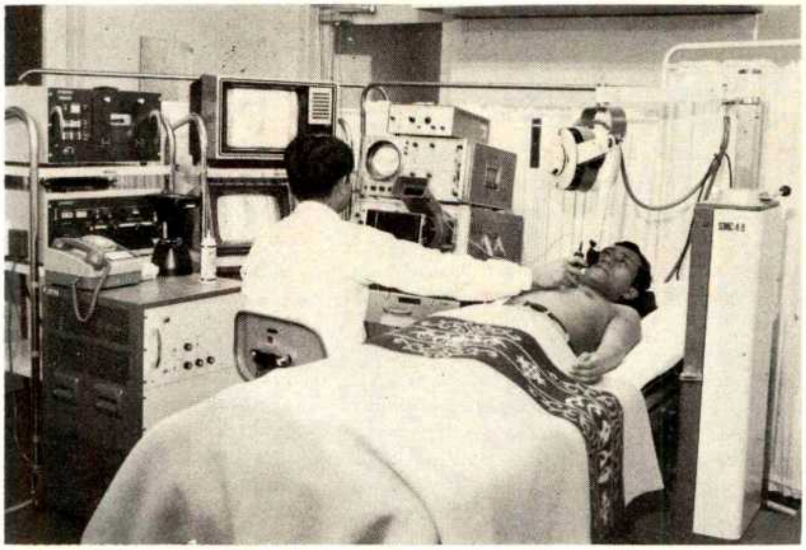


FIG. 1 *An echocardiographic examination using commercially available ultrasono-cardio-tomograph. The transducer is attached to the end of the guide arm giving reference to its position and angle and rotated and moved slowly for scanning. The equipment is connected to a device with delay and gate circuits triggered by the electrocardiogram.*

set at a predetermined phase of a cardiac cycle by the delay circuit. This allowed us to record pictures at certain periods of the cardiac cycle, avoiding the blurring effect of the cardiac motion. It took about 100 beats to complete a tomographic record (Ebina *et al.*, 1967; King, 1973; Tanaka *et al.*, 1971).

The patients were examined in the supine position, during spontaneous respiration. The ultrasonic scans were along the horizontal section of the heart, with the transducer near the left sternal border in the third, fourth, and fifth intercostal space to obtain the tomogram and M-mode scan.

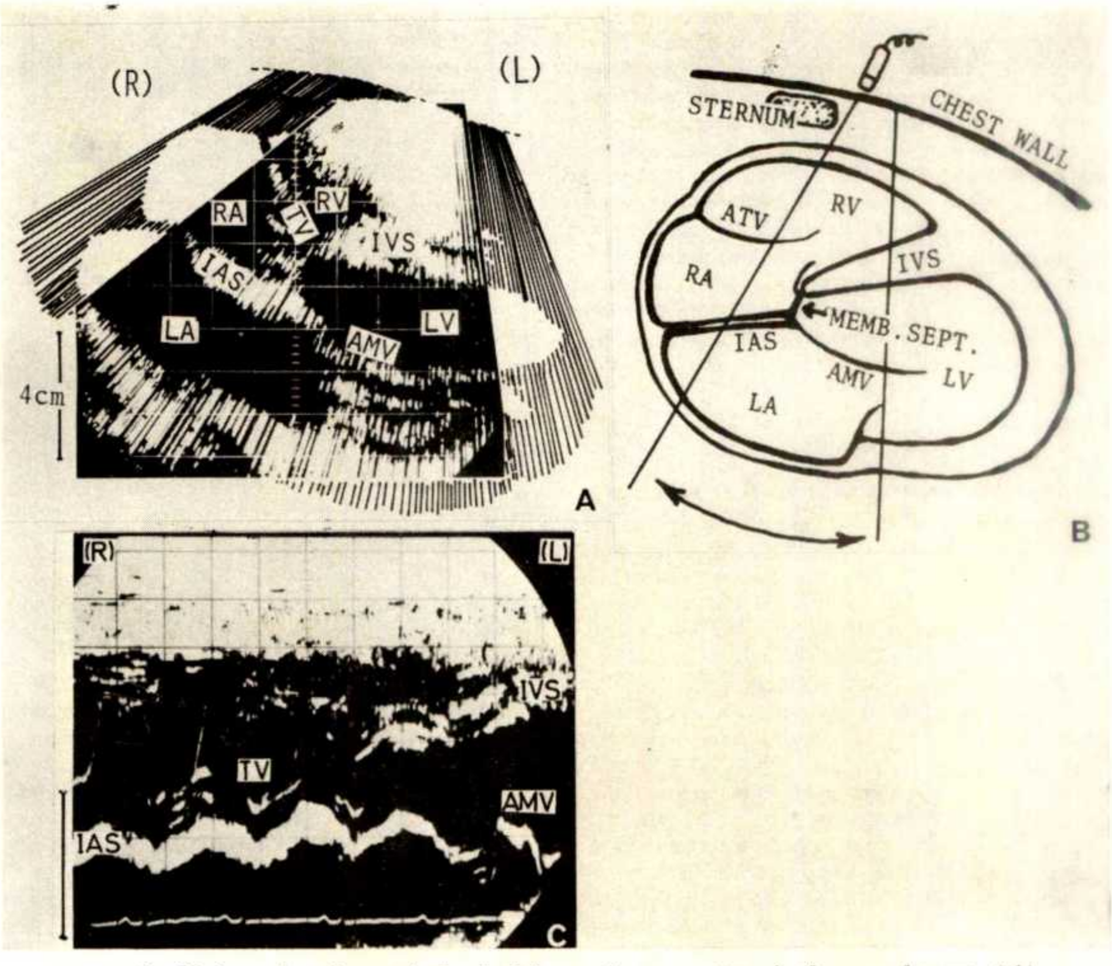


FIG. 2 *Horizontal section at the level of the membranous septum in the normal group. (A) A tomogram, viewed from the caudal side, in late systole. The interventricular septum, the interatrial septum, the tricuspid valve, and the anterior mitral valve were seen. The anterior mitral valve leaflet is continuous with that of the interatrial septum without interruption. The membranous septum, connecting the interventricular septum and the interatrial septum, was not clearly recorded. (B) A schematic drawing of the horizontal section of the heart. (C) An M-mode scan from the right to the left of the heart in the same plane as the tomogram. As observed in the tomogram, the interatrial septum connects with the anterior mitral valve leaflet behind the medial end of the interventricular septum. IVS = interventricular septum; IAS = interatrial septum; TV = tricuspid valve; AMV = anterior mitral valve; RV = right ventricle; RA = right atrium; LV = left ventricle; LA = left atrium; MEMB. SEPT. = membranous septum. (A 63-year-old woman with congestive cardiomyopathy.)*

Echoes on the tomogram were identified by reference to the motion patterns of corresponding echoes in the standard echocardiograms which were recorded with fixed beams in the area of the above-mentioned section.

Twelve patients with endocardial cushion defect ranging in age from 2 to 27 years were examined before and after operation. The diagnosis was confirmed by operation in each case, indicating that two of them were of complete form (patent ostium primum with ventricular septal defect) and the others of partial form (patent ostium primum without ventricular septal defect). The size of the ventricular septal defect, when present, was less than 5 mm in diameter. For comparison, 20 healthy subjects, 18 cases of mitral valvular disease, 4 cases of congestive cardiomyopathy, and 1 case of partial anomalous pulmonary venous drainage were examined as the 'normal' group. In addition, 25 cases of atrial septal defect of secundum type were also examined. The diagnosis of atrial septal defect of secundum type was also confirmed at operation.

## Results

### (1) General features in control groups

**(A) Normal group** Horizontal tomograms were recorded at the levels of several intercostal spaces. Firstly, the section was selected where the echo of the anterior mitral valve was clearly recorded. At this level, echoes from the anterior mitral valve and the interventricular septum were recorded in all cases, but those from the tricuspid valve and the interatrial septum were not recorded clearly in healthy subjects, as they were located behind the sternum. However, they were detected fairly well in cases with cardiac enlargement, due, for example, to congestive cardiomyopathy (Fig. 2A and 2B), particularly when right heart enlargement was present, such as with mitral valvular disease with tricuspid regurgitation. The echoes of the interventricular septum, the anterior mitral valve, the interatrial septum, and the tricuspid valve, running from left anterior, left posterior, right posterior, and right anterior, respectively, all seemed to approximate to one another. The echo of the membranous septum, which lies between the interventricular septum and the interatrial septum, was not usually recorded clearly. The echo of the interatrial septum was continuous with that of the anterior mitral valve in every case.

In the M-mode scan on the same section as the above tomogram, the continuity of the interatrial septum with the anterior mitral valve was also noted (Fig. 2C).

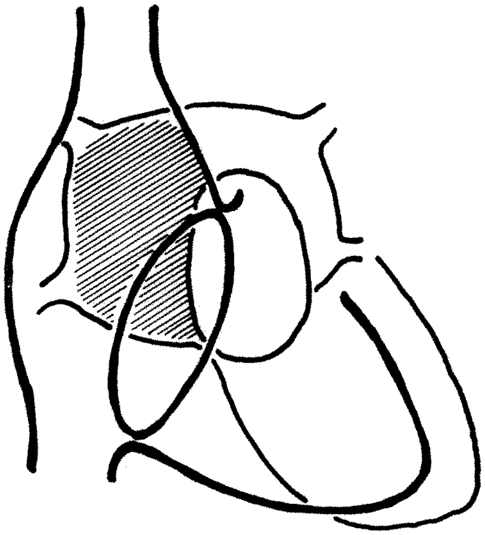


FIG. 3 *A schematic drawing of the anatomical relation between the right and left atria. The bold line indicates the right atrium and ventricle and the tricuspid annulus. The thin line shows the left atrium and ventricle and the mitral annulus. The interatrial septum indicated by the cross-hatched area is located in the upper part of the heart.*

The interatrial septum is located in the cranial part in the right atrial cavity (Fig. 3). Therefore, when the level of the horizontal section was too low (caudal), even if the ultrasound beam reached medially enough behind the sternum, the echo of the interatrial septum could not be detected. In other words, the lower the scanning section, the more posterior was the echo of the interatrial septum in the atrial cavity, eventually being inseparable from that of the posterior atrial wall. At this level, the echo of the interventricular septum ran from left anterior to right posterior joining that of the posterior wall with the mitral valve echo (Fig. 4).

If the level of the section was too high (cranial), the echo of the aorta was recorded, and the anterior mitral valve echo was continuous not with that of the atrial septum, but medially with that of the posterior wall of the aorta.

It was thus necessary to determine the level of the section for scanning carefully when examining cases of atrial septal defect of either secundum or primum type.

**(B) Atrial septal defect of secundum type** In the horizontal tomogram, the echo of the anterior mitral valve was continuous with that of the atrial

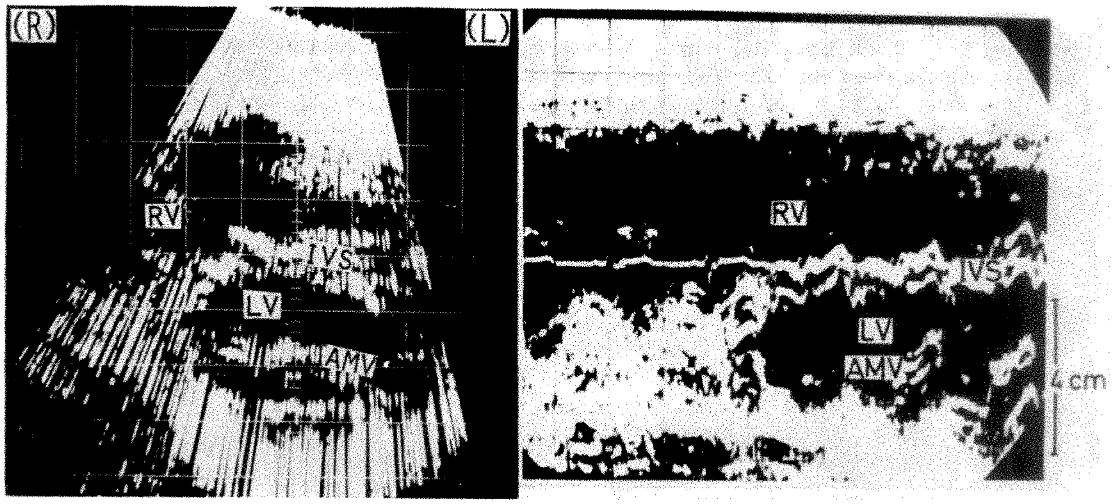


FIG. 4 *Horizontal echocardiograms at the lower (caudal) level in the normal group. (A) A tomogram, viewed from caudal side, in late systole. The level of the section is almost at the mid portion of the left ventricle. The anterior mitral valve echo did not connect with the interatrial septum but with the posterior left ventricular wall along with that of the interventricular septum. (B) : An M-mode scan at the same level as in (A). The interventricular septum emerged from the posterior left ventricular wall. These observations indicate that the echocardiographic recording at this level does not allow visualization of continuity between the interatrial septum and the anterior mitral valve. (A 14-year-old boy with partial anomalous pulmonary venous drainage.)*

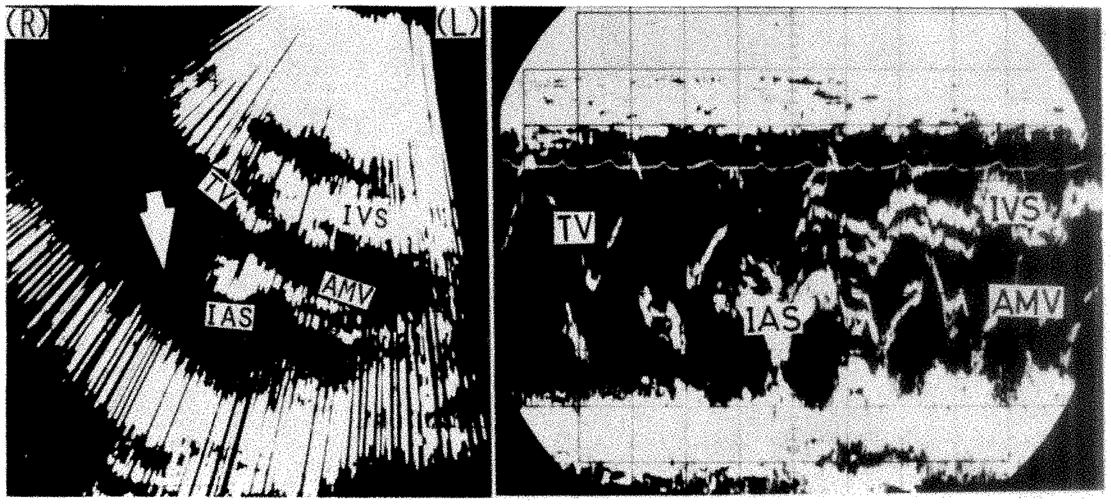


FIG. 5 *Horizontal echocardiograms at the level of the membranous septum in atrial septal defect of secundum type. (A) A tomogram, viewed from caudal side, in late systole. The anterior mitral valve was connected to the interatrial septum behind the medial end of the interventricular septum. The interatrial septum was abruptly interrupted in the middle of the atrial area (indicated by the white arrow). (B) An M-mode scan from the right to the left. The echo of the interatrial septum discontinued in the middle of the atrial area. Before complete appearance, it was recorded only during diastole, probably because the ultrasound beam grazed the rim of the defect during diastole, but not during systole, because of the movement of the heart. The connexion between the interatrial septum and the anterior mitral valve was normal. (A 22-year-old woman.)*

septum as in the normal group. However, in the middle part of that from the interatrial septum, there was an interruption (Fig. 5A). Exactly analogous findings were demonstrable on the M-mode scan (Fig. 5B).

This interruption was detected in all 25 cases of atrial septal defect of secundum type, but was never found in the normal group.

### (2) Endocardial cushion defect

In the horizontal tomogram, the mitral valve ring was closer to the medial end of the interventricular septum than in the control groups, and ended abruptly, being separated from that of the interatrial septum in all cases examined (Fig. 6A and 6B and 7A). The echo of the anterior tricuspid valve leaflet was distinctly recorded and its relation to the interventricular septum was the same as that of the control groups. The tip of the tricuspid valve echo approximated to the medial end of the interventricular septum echo during systole (Fig. 6A) and separated from it during diastole (Fig. 6B). In three cases, the echo of the interatrial septum could be shown to arise from the atrial posterior wall and to be discontinuous with that of the anterior

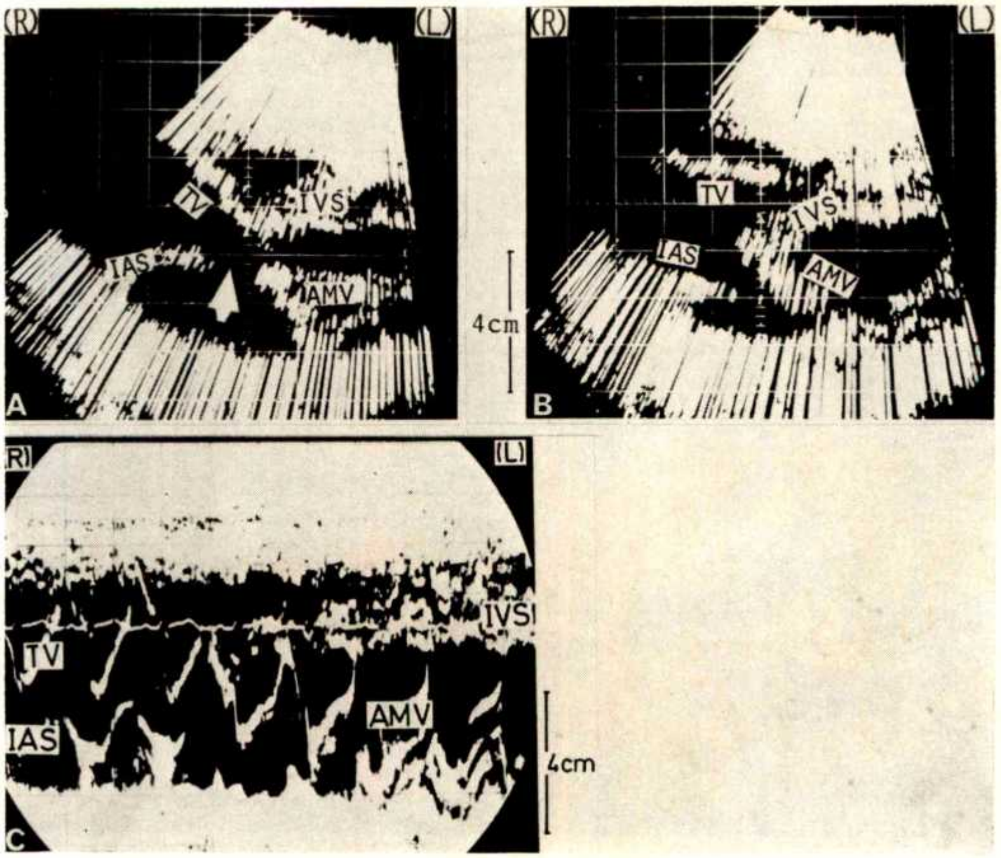
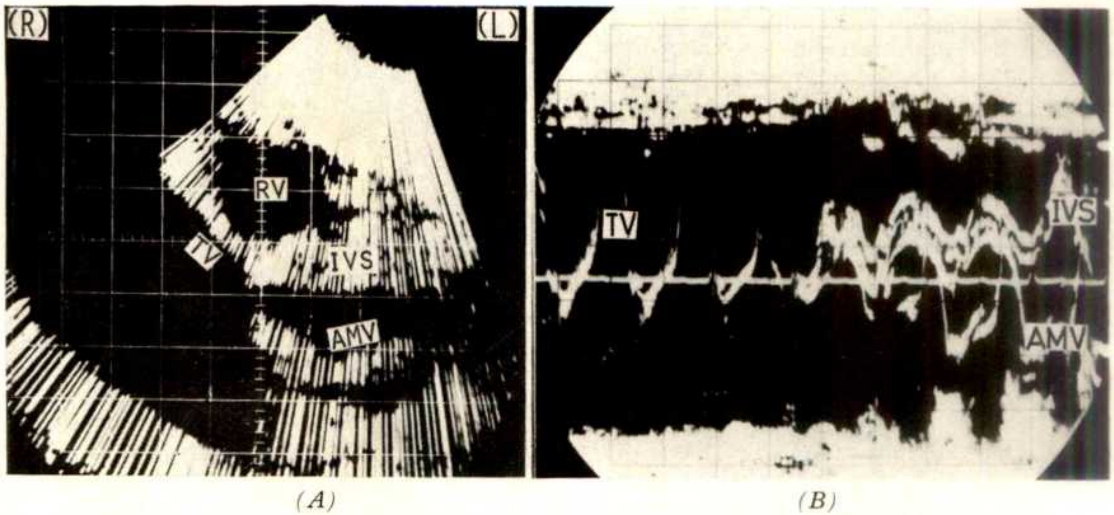
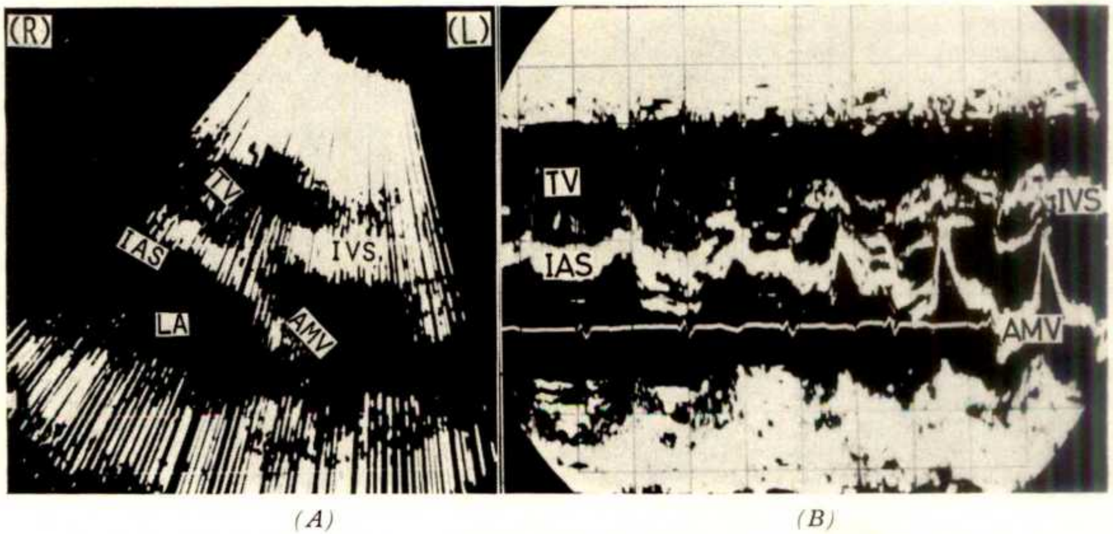


FIG. 6 *Horizontal echocardiograms at the level of the membranous septum in endocardial cushion defect. (A) A tomogram at late systole. The base of the anterior mitral valve leaflet was close to the medial end of the interventricular septum. An interruption (indicated by the white arrow) was visualized between echoes from the interatrial septum and the anterior mitral valve leaflet. (B) A tomogram at mid diastole. The mitral and tricuspid valves were in the open position. The tip of the tricuspid valve is separated from the medial end of the interventricular septum. (C) An M-mode scan from the right to the left. The interatrial septum abruptly disappeared in the atrial area, and there was no continuity between the interatrial septum and the anterior mitral valve. (A 15-year-old girl with partial form of endocardial cushion defect.)*



(*A*) (*B*)

FIG. 7 *Horizontal echocardiograms at the level of the membranous septum in endocardial cushion defect (another example). (A) A tomogram at late systole. The annular end of the anterior mitral valve was recorded close to the medial end of the interventricular septum and was not connected to the interatrial septum, as in Fig. 6. However, the interatrial septum was not recorded. (B) An M-mode scan from the right to the left. The interatrial septum was not detected. The other findings were the same as those in Fig. 6. (A 27-year-old woman with the partial form of endocardial cushion defect.)*



(*A*) (*B*)

FIG. 8 *Horizontal echocardiograms in endocardial cushion defect after surgery. (A) A tomogram viewed from caudal side. (B) An M-mode scan from the right to the left. These echocardiograms revealed the artificial interatrial septum connecting to the anterior mitral valve without interruption. (A 22-year-old woman with the partial form of endocardial cushion defect.)*

mitral valve (Fig. 6A and 6B). In the other cases, however, this was not detected (Fig. 7A).

The M-mode scan recorded in the same section showed similar findings to those obtained from the tomograms. The echo of the anterior mitral valve apparently emerged from that of the interventricular septum (Fig. 6C and 7B). The echo of the anterior tricuspid valve often appeared to be continuous with that of the anterior mitral valve (Fig. 6C and 7B). In the same 3 patients as in the tomograms the echo of the interatrial septum was recorded as being separate from the anterior mitral valve (Fig. 6C), while in the remainder, this was not detected (Fig. 7B).

After surgical repair of the interatrial septal defect, the echo of the artificial interatrial septum was recorded as being continuous with that of the anterior mitral valve (Fig. 8). The relation between the anterior mitral valve and the interventricular septum was the same as that preoperatively in all cases examined (Fig. 8).

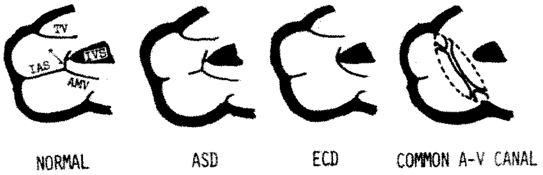


FIG. 9 *Schematic drawings of horizontal section of the normal heart, atrial septal defect of secundum type, endocardial cushion defect, and common atrioventricular canal. The membranous septum (*) connects the interventricular septum, the septal tricuspid valve, the interatrial septum, and the anterior mitral valve. In the case of atrial septal defect of secundum type (ASD), the membranous septum is normal, and there is a defect in the middle part of the interatrial septum. In endocardial cushion defect (ECD), the membranous septum is not developed. The septal leaflet of the tricuspid valve and the anterior mitral valve leaflet are directly attached to the interventricular septum, so that there is no continuity between the interatrial septum and the anterior mitral valve leaflet. In common atrioventricular canal (COMMON A-V CANAL), an extreme form of endocardial cushion defect, the septal leaflet of the tricuspid valve and the anterior part of the anterior mitral valve are fused together to form a single leaflet, which is not connected to the interatrial septum.*

## Discussion

Exaggerated anterior mitral valve excursion traversing the interventricular septum, prolonged mitral-septal apposition, a narrow left ventricular outflow tract, paradoxical movement of the interventricular septum, and increased right ventricular dimension have recently been reported as characteristic echocardiographic features of endocardial cushion defect (Gramiak *et al.*, 1972; Sahn *et al.*, 1974; Pieroni *et al.*, 1975). Moreover, using the technique of M-mode scan along the longitudinal axis of the heart, Williams and Rudd (1974) noted that the echo of the anterior mitral valve emerged from that of the anterior border of the left ventricular outflow tract. Each of these findings, which were also obtained in our study, is not sufficient on its own to confirm the diagnosis of endocardial cushion defect, because they are not always found in cases of endocardial cushion defect (Sahn *et al.*, 1974). In order to diagnose endocardial cushion defect, therefore, the site of the atrial septal defect should be demonstrated. In the present study, this was shown as a discontinuity between the echo of the anterior mitral valve and that of the atrial septum in the horizontal section in all cases examined. This discontinuity was never detected in patients with other types of heart disease including those with atrial septal defect of secundum type, and it directly reflected the anatomical basis of the atrial septal defect of endocardial cushion defect (Fig. 9).

It is important in clinical practice to differentiate between endocardial cushion defect and secundum type of atrial septal defect. In the case of secundum atrial septal defect the endocardial cushion is developed completely, so that the relation between the atrial septum and the anterior mitral valve leaflet is normal, the defect itself being located in the middle of the atrial septum (Fig. 9). These anatomical features were demonstrated by the tomogram, which showed the anterior mitral valve leaflet to be continuous with that of the interatrial septum in the horizontal plane, while the defect itself was represented by an interruption in the middle part of the atrial septum (Fig. 5). Thus, the difference in the site of the interruption of the echo in the scan from the anterior mitral valve to the interatrial septum corresponded to the anatomical difference between the two types of atrial septal defect, and its demonstration makes the essential differential diagnosis by ultrasound. In our laboratory, we have never failed in a diagnosis of endocardial cushion defect, either false positive or false negative, using these criteria.

Another malformation in endocardial cushion defect is abnormal attachment of the anterior mitral valve. The anterior mitral valve does not attach to the membranous septum, but to the interventricular septum directly, because the endocardial cushion is undeveloped (Fig. 9). In the present study, the echo of the base of the anterior mitral valve leaflet was recorded close to that of the medial end of the interventricular septum in all cases of endocardial cushion defect in comparison with that in the control groups, and this relation was not altered by corrective surgery. This finding corresponds to the abnormal attachment of the anterior mitral valve. In the control groups, on the other hand, the base of the anterior mitral valve leaflet was some distance from the medial end of the interventricular septum, the gap corresponding to the membranous septum.

Another feature of endocardial cushion defect is a cleft mitral valve. Sahn *et al.* (1974) presented multiple echoes in the mitral area on the echocardiogram and Pieroni *et al.* (1975) showed multiple representation of the systolic image of the mitral valve as an indication of the mitral cleft. In the present study, such echocardiographic findings were obtained in some cases with mitral cleft, which were confirmed later by surgery. However, these findings were not considered to represent features which were specific to the mitral cleft since repair of the cleft with 'teflon' or pericardium did not always eliminate these abnormal echoes, and since a similar echocardiographic pattern was obtained in cases of mitral valve disease or even congestive cardiomyopathy (personal observation). It is considered that further examination is necessary to differentiate one from the other.

The difference between complete and incomplete forms, i.e. the presence of the defect of the interventricular septum, was not detected in the present study. The defect of the interventricular septum in our cases was less than 5 mm in diameter, so that it was probably not detected on account of insufficient resolution of the equipment. In the case of an extreme form of endocardial cushion defect (common atrioventricular canal), the septal tricuspid valve and the anterior part of the anterior mitral valve are fused together to form one large leaflet (Fig. 9). Of cases examined in the present study, the M-mode scan along the horizontal section gave an apparent continuity between the anterior tricuspid valve and the anterior mitral valve, erroneously suggesting that two valves were fused together even in cases of partial form. However, the tomogram revealed that the anterior tricuspid valve was separate anteriorly from the interventricular septum during diastole (Fig. 6B), and displayed the individual movement of those two valves. Therefore, such continuity on the M-mode scan does not always indicate the common atrioventricular valve. This apparent continuity might be caused by the direct attachment of the anterior mitral valve to the interventricular septum, since the anatomical relation between the anterior tricuspid valve and the interventricular septum was normal. Careful interpretation should be made when the M-mode scan gives apparent continuity or discontinuity between echoes, as discussed recently by French and Popp (1975) in another context.

In summary, horizontal echocardiographic searching at the level of the membranous septum is useful in the diagnosis of endocardial cushion defect and in the differentiation of this malformation from atrial septal defect of secundum type. The definitive diagnosis of endocardial cushion defect can be made when the echocardiogram reveals the discontinuity between the anterior mitral valve and the interatrial septum.

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# Prognosis in unstable angina[1]

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*A retrospective study was made of 158 patients with unstable angina admitted to a coronary care unit over a 4-year period. Twenty patients (13 per cent) had myocardial infarcts while in hospital, and of these 3 died; three others died without preceding evidence of myocardial infarction. There was thus an acute mortality rate of 4 per cent. Patients with persisting angina after the first 24 hours and those without a previous history of myocardial ischaemia were more likely to develop a myocardial infarct or to die in hospital.*

*Follow-up information, ranging from 3 to 7 years, was available in 144 of 152 hospital survivors. Patients older than 60 years ($P<0.05$), with cardiomegaly ($P<0.01$) and with pulmonary venous congestion ($P<0.05$) were found to have significantly increased long-term mortality. Long-term mortality was also found to rise with increasing coronary prognostic index. The average mortality rate for the whole group of hospital survivors was about 5 per cent per annum. Of the 111 patients who were alive at follow-up, 19 (17%) had had a myocardial infarct after leaving hospital, and a similar number had moderate or severe angina.*

Many patients with acute myocardial infarction describe a change in the character of angina before the event (Sampson and Eliaser, 1937); the symptom either deteriorates from a previously stable pattern, or recurs after a period of freedom from chest pain. Interest in this phenomenon has arisen because of the possibility that it may herald impending myocardial infarction, the consequences of which might be averted by prompt treatment. Thus, there have been previous trials with anticoagulation therapy (Nichol, Phillips, and Casten, 1959; Wood, 1961); more recently, attention has been directed at emergency myocardial revascularization (Dunkman *et al.*, 1974). At present, however, the place of surgery in unstable angina is uncertain, in part because the long-term prognosis of patients with the condition has not been well documented. Only one previous study has described a follow-up of over 5 years (Gazes *et al.*, 1973). In order to obtain more information on the short and long-term outlook of patients with unstable angina, and the clinical factors that might influence prognosis, we have retrospectively studied a group of such patients admitted to a coronary care unit.

## Patients and methods

Hospital records of patients admitted to the Green Lane Hospital Coronary Care Unit (CCU) over a four-year period (March 1967 to March 1971) were examined for patients who satisfied our criteria for unstable angina.

Unstable angina was considered to be present if patients had ischaemic cardiac pain at rest or with minimal exertion occurring within 4 weeks before admission, either for the first time, or after a period of stable angina. In all patients, the symptoms had been sufficiently severe to warrant admission to the hospital, and were either crescendo in nature, or associated with one or more prolonged bouts of chest pain lasting up to 30 minutes. These patients were all admitted to the CCU. Patients with significant arrhythmias, severe valvular disease, or evidence of myocardial infarction occurring less than 4 weeks before admission or for up to 48 hours after admission were excluded. Myocardial infarction was diagnosed if, in addition to the characteristic ischaemic pain, at least one of the following two criteria were fulfilled: (a) pathological Q waves, ST segment elevation, or T wave inversion with

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evolutionary changes; (b) rise in serum aspartate aminotransferase to over 40 units/ml. Patients who had had previous myocardial infarction or angina for more than 4 weeks were considered to have a previous history of ischaemic heart disease.

From the case notes of these patients details were noted of the following: previous history of ischaemic heart disease, cigarette smoking, hypertension, and diabetes; admission chest *x*-ray film; serial electrocardiograms; biochemical data; persistent chest pain in hospital; and details of medical treatment. The chest *x*-ray films, the majority of which were standard five-foot anteroposterior films taken using portable apparatus, were all obtained within 24 hours after admission, and were examined for heart size and presence of pulmonary congestion by one radiologist (J.B.P.) who had no knowledge of the clinical outcome of the patients in the study; the presence of cardiomegaly was assessed by a method described previously (Norris *et al.,* 1969). Persisting chest pain was considered present if the records indicated that chest pain was present for three or more days after the first 24 hours in hospital, despite adequate bed rest and in most cases administration of nitroglycerin and beta-adrenergic blocking drugs.

To obtain follow-up information, a standard questionnaire was sent to the referring doctors in June 1974 inquiring about the symptomatic status of the hospital survivors with particular regard to angina, or the date and cause of death. If this approach failed, either the patients or their relatives, friends, or neighbours were traced, and information obtained by either interviewing or writing to them. In cases where the details of death were incomplete, further information was obtained from death certificates at the Registry of Deaths in Auckland. Of the survivors who were traced in this manner, the median follow-up was 5 years, range 3 to 7 years.

Results were analysed statistically using the $\chi^2$ test and differences were considered significant when $P < 0{\cdot}05$ for the two-tailed test.

## Results

There were 1757 admissions to the CCU during the four-year period; 158 patients (9%) had unstable angina by our criteria. Of these, 109 were men and 49 women; the average age was 55 years. Thirty-four patients had no previous history of ischaemic heart disease; of the 124 patients who had such a history, 40 had no past history of myocardial infarction, while 84 had had one or more myocardial infarcts in the past.

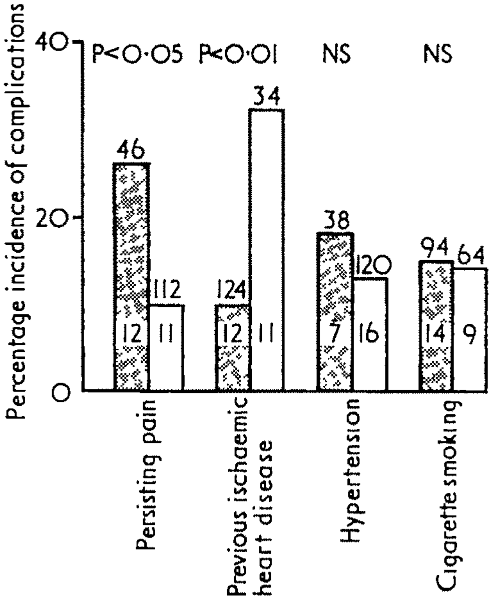

FIG. 1 *Clinical factors related to the occurrence of myocardial infarction or death in hospital. Shaded bars refer to patients with the factors under consideration, and unshaded bars to patients without these factors. The number of patients at risk are indicated above, and the number with complications inside each bar.*

TABLE *Serious complications in hospital*

| *Complications* | *No. of cases* | *Deaths* |
|---|---|---|
| Myocardial infarction | 20 | 3 |
| Sudden death without preceding evidence of myocardial infarction | 3 | 3 |

### Complications in hospital

The incidence of myocardial infarction and death in hospital is shown in the Table. Twenty patients (13%) had myocardial infarcts occurring from 48 hours to 3 weeks after admission to hospital, and of these 3 died. Three other patients died without preceding evidence of myocardial infarction, 2 suddenly and 1 from pulmonary embolism. Necropsy of these 3 patients showed no evidence of fresh myocardial infarction in the first 2 patients, and confirmed massive pulmonary embolism in the third. The mortality rate in hospital was thus 4 per cent.

Fig. 1 examines some clinical factors which

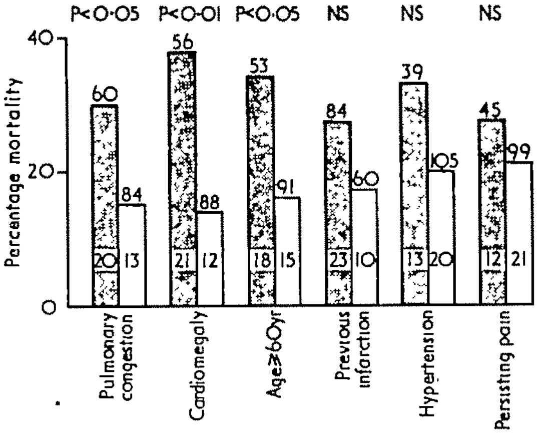

FIG. 2 *Clinical factors related to long-term mortality. Shaded bars refer to patients with the factors under consideration, and unshaded bars to patients without these factors. The numbers of patients at risk are indicated above each bar, and the number of patients who died after leaving hospital inside each bar.*

might be associated with the occurrence of either myocardial infarction or death in hospital. Patients who had persisting pain after the first 24 hours ($P < 0{\cdot}05$), and those without a previous history of ischaemic heart disease ($P < 0{\cdot}01$) were more likely to have a bad short-term prognosis. A history of hypertension or cigarette smoking, however, was not associated with increased risk.

## Long-term follow-up

Follow-up information was available in 144 of 152 hospital survivors (95%). This was examined for the presence of factors which might influence the long-term prognosis (Fig. 2). The risk of dying after leaving hospital was found to be associated with age greater than 60 years ($P < 0{\cdot}05$), cardiomegaly ($P < 0{\cdot}01$), and pulmonary congestion ($P < 0{\cdot}05$) as judged from the admission chest *x*-ray film. A history of previous myocardial infarction, hypertension, and the presence of persistent chest pain in hospital were also associated with increased long-term mortality, but the differences did not reach statistical significance.

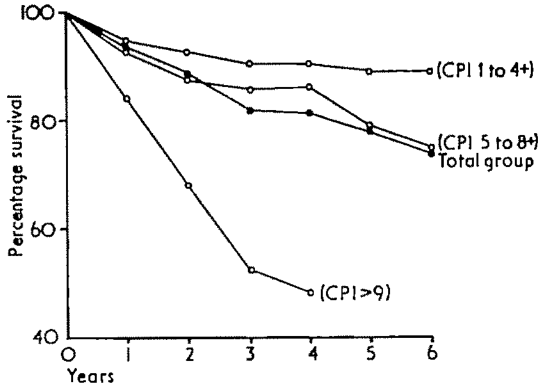

FIG. 3 *Follow-up of 144 hospital survivors, showing cumulative mortality rate related to the coronary prognostic index. The rate for the group with CPI > 9 was not plotted after 4 years, as the number of survivors was too small.*

Since 4 of these factors (age, cardiomegaly, radiological evidence of pulmonary congestion, and a past history of myocardial infarction) are used in a previously described coronary prognostic index (CPI) for long-term survival (Norris *et al.*, 1970), it was of interest to relate the long-term mortality to the CPI of the hospital survivors. Fig. 3 shows the cumulative annual mortality rate for 3 groups of patients with increasing CPI. It is apparent that mortality rises with increasing CPI. The cumulative mortality of the group with CPI greater than 9 ($n = 25$) was significantly greater than that of the group with CPI 1 to 4+ ($n = 65$) after 2 years ($P < 0{\cdot}01$) and that of the group with CPI 5 to 8+ ($n = 54$) after 3 years ($P < 0{\cdot}005$). The difference in the cumulative mortality rates between the group with CPI 1 to 4+ and that with CPI 5 to 8+ did not reach statistical significance. The yearly mortality rate was about 2 per cent for patients with CPI 1 to 4+, 5 per cent for patients with CPI 5 to 8+, and 13 per cent for patients with CPI > 9. The average mortality rate for the whole group was about 5 per cent over the 6-year period of follow-up.

Of the 111 hospital survivors who were alive at the time of follow-up, 19 (17%) have had a subsequent myocardial infarct. Nineteen patients were found to have moderate to severe angina, i.e. angina occurring with mild exertion or interfering with work or normal activities.

## Discussion

One of the particularly difficult areas in clinical cardiology today is the management of unstable angina. Recently, Fowler (1971) called for a widely acceptable objective definition of the condition, and stressed that this should include recent onset angina from a background of good health, a change in the symptomatic pattern of previously recognized ischaemic heart disease, and angiographic confirmation of coronary artery obstruction. The patients in our study satisfy the clinical criteria suggested, but must be regarded as a selected group in that the nature of the symptoms was such that admission to the hospital was considered necessary. The lack of angiographic data in our study is a disadvantage, but many of these patients were admitted when coronary angiography was either not performed in Green Lane Hospital or was in its infancy there. Furthermore, we were interested in long-term follow-up information, and to have this in conjunction with angiographic data would obviously have required many more years to obtain.

For a number of years, interest in unstable angina has resulted from the possibility that the pattern of changing symptoms might be a warning of impending myocardial infarction. Four weeks after admission, 13 per cent of our patients had developed acute myocardial infarcts, and 4 per cent had died. These results are comparable with those reported recently by others (Fulton *et al.,* 1972; Krauss, Hutter, and De Sanctis, 1972; Gazes *et al.,* 1973) who observed an incidence of myocardial infarction varying from 6 to 17 per cent and an acute mortality rate from 1 to 8 per cent. Our study showed that patients without a previous history of ischaemic heart disease, and those with persisting angina in hospital, appeared to be at increased risk from either infarction or dying in hospital. The former finding was unexpected, and may be the result of a tendency in our centre for patients with known heart disease to be referred preferentially for admission. The observation that patients with persisting angina unrelieved by medical treatment form a high risk group has been made previously (Gazes *et al.,* 1973; Fischl, Herman, and Gorlin, 1973).

The mortality rate of patients with unstable angina in our study was about 5 per cent annually. This might have been higher if coronary angiography had been performed, and patients with normal coronary arteries excluded. The only other study with a long-term follow-up (Gazes *et al.,* 1973) reported an annual mortality of 8 per cent in the first 5 years, and 5 per cent over 10 years. The mortality rate for unstable angina is thus not dissimilar to the annual mortality of 4 per cent reported for patients with stable angina (Frank, Weinblatt, and Shapiro, 1973).

The results of the present study have shown that, as in the case of patients with completed infarction (Norris *et al.,* 1970), long-term survival of patients with unstable angina can be predicted by analysis of clinical factors measurable on admission to hospital. Thus, increasing age, cardiomegaly, and left ventricular failure significantly and adversely affected long-term prognosis, while there was also a tendency for a previous history of ischaemic heart disease and hypertension to predict an unfavourable outcome.

Despite minor differences in the definition of unstable angina, our results agree with those of recent studies (Fulton *et al.,* 1972; Krauss *et al.,* 1972; Gazes *et al.,* 1973) with regard to long-term mortality and incidence of myocardial infarction and death in the acute stage. These results indicate that in the context of ischaemic heart disease the prognosis of patients with unstable angina is not particularly grave. The mortality rate in the acute stage is also comparable with that described for patients treated surgically, which ranged from no mortality (Auer *et al.,* 1971; Bolooki *et al.,* 1974) to 10 per cent (Miller *et al.,* 1973). In studies where randomization of surgical and medical treatments was attempted (Bertolasi *et al.,* 1974; Kloster *et al.,* 1975), no significant difference in acute mortality between surgery and conservative manage-was noted. The effect of surgery on the long-term mortality of unstable angina, however, is at present uncertain, but compared with medical treatment a higher proportion of surgically-treated patients with unstable angina was reported to be symptomatically improved on follow-up in randomized (Bertolasi *et al.,* 1974; Kloster *et al.,* 1975) and non-randomized studies (Scanlon *et al.,* 1973; Conti *et al.,* 1973). These considerations suggest that there is no strong indication for emergency myocardial revascularization for such patients, and that elective surgery should be reserved for patients whose symptoms are unresponsive to medical treatment.

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# Tetralogy of Fallot
## *Risk factors associated with complete repair*

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*Ninety-six consecutive total repairs of the tetralogy of Fallot are reviewed. There was an overall hospital mortality of 8·3 per cent and a total incidence of low output cardiac failure of 18·8 per cent, and this was the principal cause of death and the most important source of postoperative morbidity. In 49 cases there had been a previous palliative shunt procedure and there was a strikingly lower mortality and a highly significant lower morbidity in this group. Other factors which correlated in a positive fashion with increased mortality and morbidity were chronic hypoxia (as evidenced by polycythaemia), age below 5 years, severe postoperative right ventricular hypertension, and (to a lesser extent) extensive right ventricular outflow tract reconstruction.*

*Data are presented to support the hypothesis that a palliative shunt procedure should be considered in the severely polycythaemic child with a surgically 'unfavourable' right ventricular outflow. This policy carries a low early mortality in our hands (5·4%), and is associated with a low mortality (3·9%) at subsequent repair. This compares with a mortality of 12·8 per cent for primary repair, and the incidence of low output cardiac failure is five times as high in the primary repair as compared to the previously shunted group.*

The congenital heart defect which is now almost universally known as the tetralogy of Fallot was first recognized as a pathological entity by Nils Stensen in 1671. In the succeeding centuries it was known to a number of medical writers but it was not until 1888, after a series of papers by Louis-Etienne Fallot, who in fact called the condition 'Cyanose Cardiaque', that the clinical and pathological features were clearly described and correlated. This author drew attention to four cardinal features of the condition in such a clear and concise fashion that the eponym, 'Fallot's tetralogy', seems to be a fitting memorial.

In 1945, Blalock and Taussig first described an operation to palliate the symptoms of the condition, and the first attempt at complete repair of the lesion was made in 1954 by H. W. Scott using whole body hypothermia and circulatory arrest.

The subsequent development of safe methods of cardiopulmonary bypass has allowed refinements of surgical techniques such that the operative mortality for complete repair is now about 5 to 10 per cent in most reported series (Malm *et al.*, 1966; Gottsman *et al.*, 1969; Kirklin and Karp, 1970).

In an effort to try to recognize factors which correlate with the continuing hospital mortality, we have reviewed the results achieved in a consecutive series of 96 operations conducted during a 4-year period.

### Subjects and methods

During the four-year period ending in 1974, all operations for total repair of the tetralogy of Fallot have been reviewed. The data recorded included age at operation, weight centile using hospital graphs derived from data by Tanner, Whitehouse, and Takaishi (1966), history of a previous shunt procedure, haemoglobin level in g/dl, method of outflow tract reconstruction, the ratio of right ventricular to left ventricular systolic pressure measured at the conclusion of the operation, total cardiopulmonary bypass time, blood loss in the first 6 postoperative hours expressed as ml/kg per hr, mean systolic blood pressure during the first 24 postoperative hours, urine flow during the first 24 postoperative hours expressed as ml/kg per hr,

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and the subsequent postoperative course in hospital.

The two morbidity end-points which were considered were (1) death in hospital and (2) low output cardiac failure. This latter end-point was a clinical diagnosis which was arbitrarily defined by the following features: (1) cool, cyanosed extremities; (2) systolic blood pressure less than 90 mmHg (12 kPa) for the initial 24 hours after operation; (3) urine flow less than 0·7 $\mathrm{ml/kg^{-1}\,hr^{-1}}$ for the whole of the 24-hour period; and/or (4) the necessity for a catecholamine infusion to overcome the clinical signs listed as 1 to 3 above

Preoperative and intraoperative observations were correlated with the two morbidity end-points and, in part, with each other. The significance of observed correlations was tested by standard statistical methods (Snedecor and Cochran, 1967).

## Operative techniques

The techniques used during the operation and perfusion were substantially the same for all cases during the period under review. Perfusions were conducted with haemodiluted primes, a bubble oxygenator, a roller pump, and the nasopharyngeal temperature was reduced to 25°C. Intracardiac manoeuvres were carried out with intermittent periods of aortic cross-clamping up to 20 minutes at any one time. The left ventricle or the left atrium was vented. The ventricular septal defect was patched with two-way stretch knitted 'dacron' material. Right ventricular outflow tract patches, when used, were generally of autogenous pericardium, and in a few cases a monocusp valve was fashioned to provide at least temporary pulmonary valve competence. Right atrial and central arterial pressures were monitored postoperatively in all patients, and left atrial pressure was monitored also on some occasions. Postoperative management was along conventional lines and catecholamine infusion was usually the first drug intervention used if a low cardiac output was diagnosed.

TABLE 1 *Mortality in 96 consecutive cases of total repair of Fallot's tetralogy*

| | *Cases* | *Mortality* |
|---|---|---|
| Primary repair | 47 | 6 (12·8%) |
| Previous shunt | 49 | 2 (3·9%) |
| Total | 96 | 8 (8·3%) |

(0·30>P>0·20)

## Results

### Influence of prior shunt on results of complete repair

The overall results in relation to hospital mortality are shown in Table 1. This shows that the overall mortality for all 96 operations was 8·3 per cent. The mortality was considerably higher in the unshunted as compared with the previously shunted group though the difference on these figures was not statistically significant.

The causes of death in the 8 fatal cases are listed in Table 2. The mode of death in all 8 cases was low output cardiac failure as defined above, but in the two previously shunted patients there seemed to be a demonstrable cause for this in that unrecognized obstructive pulmonary vascular disease had supervened in one patient after a Waterston shunt and in the second case the right ventricular outflow tract obstruction had not been relieved. In the remaining 6 cases, all unshunted, there was no such discernible cause for the low output cardiac failure unless one postulates that low pulmonary flow from

TABLE 2 *Causes of death in 96 consecutive cases of total repair of Fallot's tetralogy*

| *Cause of death* | *Cases* |
|---|---|
| Low output cardiac failure | 6 (all unshunted) |
| Obstructive pulmonary vascular disease | 1 (previous Waterston shunt) |
| Unrelieved right ventricular obstruction | 1 (previous left Blalock) |
| Total | 8 |

TABLE 3 *List of previous shunt operations and mortality at subsequent repair*

| *Shunt* | | *Cases* | | *Mortality* | |
|---|---|---|---|---|---|
| Right pulmonary artery to aorta (Waterston) | | 18 | | 1 (5·5%) | |
| Left pulmonary artery to aorta (Pott's) | | 9 | | 0 | |
| Left subclavian artery to left pulmonary artery | Blalock | 8 | 22 | 1 (12·5%) | 1 (4·5%) |
| Right subclavian artery to right pulmonary artery | | 14 | | 0 | |

early life may result in a left ventricle which is not 'trained' to sustain a normal cardiac output.

In any event, for the purpose of this paper, the total mortality in this series in both shunted and unshunted cases was regarded as the result of low output cardiac failure, and statistical analyses were made on this assumption.

Table 3 lists the various types of pulmonary to systemic shunts which required to be taken down at the time of complete repair together with the operative mortality in each group. Though in our experience the technically easiest shunt to take down is a right Blalock, there is no evidence from these figures that one shunt rather than another introduces a significant risk of fatal complications at the time of complete repair.

The second analysis was to determine the total incidence of low output cardiac failure in the entire series of 96 operations. The total incidence was regarded as the fatal cases plus those non-fatal cases which met the arbitrary definition of low output failure as described above. This analysis is set out in Table 4 and shows clearly that there was 5 times the incidence of this event in the unshunted as opposed to the shunted subset; this difference was highly significant.

TABLE 4 *Incidence of low output cardiac failure*

| | *Cases* | *Cardiac failure* |
|---|---|---|
| Primary repair | 47 | 15 (31 9%) |
| Previous shunt | 49 | 3 (6·1%) |
| Total | 96 | 18 (18·8%) |

(0 005>P>0·001)

### Influence of patient age on results of complete repair

None of the patients in this series was under the age of 2 years. The distribution of patients according to age is illustrated in the bar-graph represented in Fig. 1 and the data are analysed in Table 5. The patients in the shunted group tended to be slightly older, with a median age of 8·3 years as opposed to the unshunted group with a median age of 6·1 years. The mortality and total incidence of low output cardiac failure was 2 to 3 times higher in the patients under the age of 5 years though on the figures available the significance of this difference is not certain. However, our experience suggests that patients over the age of 5 years, especially if they have a prior shunt, have a better postoperative course.

### Influence of patient's weight (physical development) on results of complete repair

The great majority of the patients in this series were much below the appropriate weight in relation to their age. This is illustrated in the bar-graph

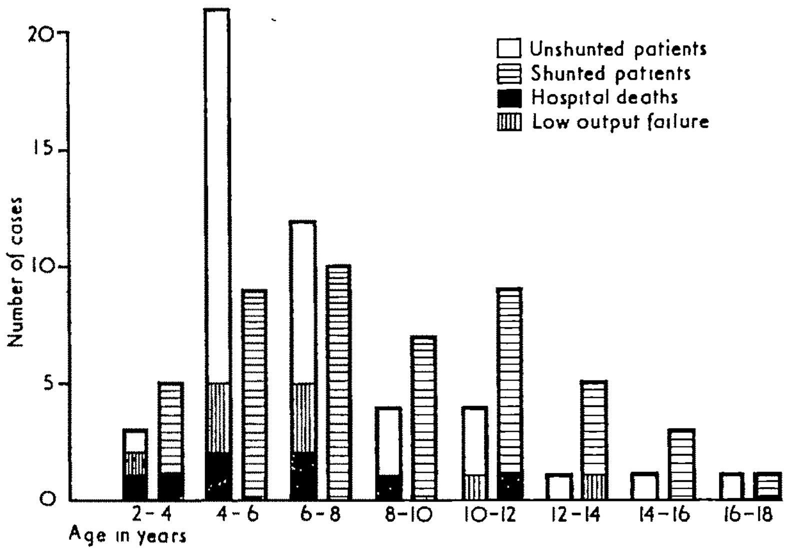

FIG. 1 *This bar graph depicts the distribution of the shunted and unshunted patients in the various age groups. The median age of the unshunted patients was 6·1 years compared with 8·3 years in the shunted patients, but this difference did not reach significant levels (0·10 > P > 0·05).*

TABLE 5 *Relation of age to mortality and power failure*

| | *Age (y)* | *No.* | *Mortality* | | *Power failure* | |
|---|---|---|---|---|---|---|
| Primary repair | <5<br>>5 | 16<br>31 | 3 (18·7%)<br>3 (10·7%) | P>0·20 | 7 (43·7%)<br>8 (25·8%) | P>0·20 |
| Previous shunt | <5<br>>5 | 9<br>40 | 1 (11·1%)<br>1 (2·5%) | P>0·20 | 2 (22·2%)<br>3 (7·5%) | P>0·20 |
| All cases | <5<br>>5 | 25<br>71 | 4 (16%)<br>4 (5·6%) | P<0·20 | 8 (32%)<br>10 (14·1%) | P<0·05 |

represented in Fig. 2. Half the patients in the unshunted group were below the 10th centile for weight, and a similar proportion in the shunted subset were below the 20th centile. This indicates that the entire group of 96 patients were much less well physically developed than the average population of their age and this difference was highly significant (P<0·001). However, there was no statistically significant difference in the distribution of the two groups, shunted and unshunted, according to weight centiles, and the mortality and morbidity seemed randomly distributed over the range of centile subgroups as is evident from Table 6. It is concluded that body weight adjusted for age has no predictive value in anticipating hospital morbidity or mortality.

## Influence of preoperative haemoglobin levels on results of complete repair

A raised haemoglobin level in these patients was taken as evidence of chronic hypoxia caused by a reduced or suboptimal pulmonary blood flow. As expected, there tended to be a higher proportion of shunted patients in the groups with normal or near normal haemoglobin levels as is illustrated in Fig. 3, though the difference in observed distribution did not reach significant levels. There was a significantly higher mortality and morbidity in the group with haemoglobin concentrations in excess of 19 g/dl. This is evident in the analysis set out in

TABLE 6 *Relation of body weight to mortality and low output cardiac failure*

| *Weight (centile)* | *All cases* | *Mortality* | *Power failure* |
|---|---|---|---|
| <10th | 44 | 6 (13·7%) | 9 (20·5%) |
| 10th–50th | 34 | 1 (3·3%) | 4 (13·2%) |
| >50th | 18 | 1 (5·6%) | 5 (20·2%) |
| | | NS | NS |

Shunted and unshunted cases appeared randomly distributed between 3 weight/centile subsets.
NS=not significant.

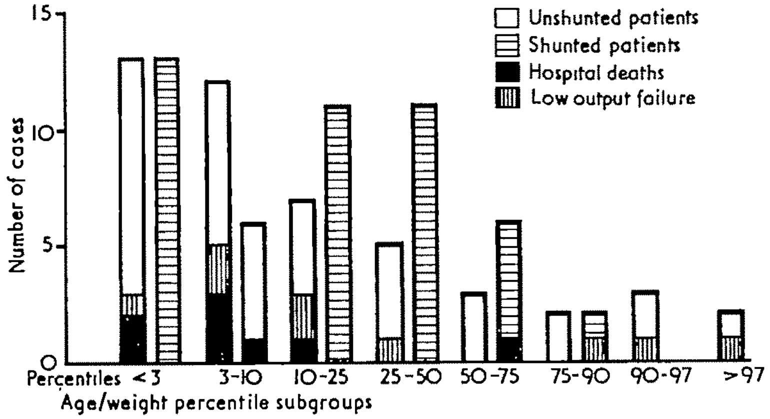

FIG. 2 *This bar graph depicts the distribution of shunted and unshunted patients according to weight centiles. There was no significant difference in the distribution of the two groups, but both distributions differed highly significantly from an expected normal population (P<0·001).*

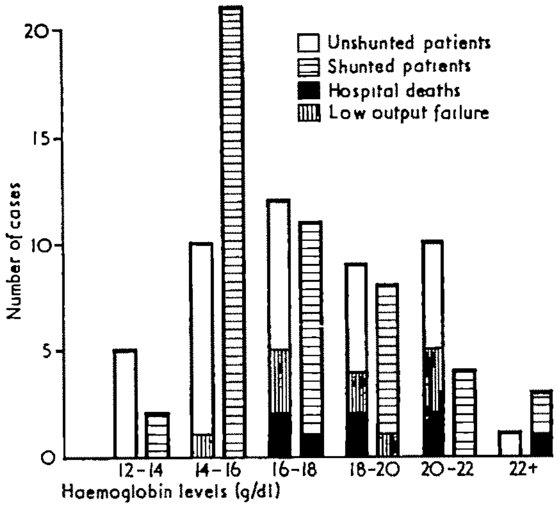

FIG. 3 *This bar graph depicts the distribution of shunted and unshunted patients according to haemoglobin levels. The median level in the unshunted group was 17·4 g/dl compared with 16·3 g/dl in the shunted group, but this difference did not reach significant levels (0·20 >P >0·10).*

Table 7 and the figures certainly support the thesis that high haemoglobin levels are associated with increased operative risk.

## Combined influence of major preoperative risk factors on results of complete repair

From the analysis thus far it seemed that earlier shunting was associated with a reduced morbidity, whereas a high haemoglobin level was associated with an increased risk. By combining these two factors (see Table 8) it was possible to define a low risk group with haemoglobin levels in the normal range, whether or not shunted, a moderate risk group who had raised haemoglobin levels but were previously shunted, and a high risk group who had both high haemoglobin levels and had not had a previous shunt. The observed difference in morbidity in these three clinical groups was highly significant.

If each of these three groups was further subdivided into subgroups below and above the age of 5 years (see Table 9), the numbers become too small to achieve statistical significance, but the mortality and morbidity in the younger age subgroups seem to be appreciably higher.

TABLE 7 *Relation of haemoglobin levels to mortality and low output cardiac failure*

| | *No.* | *Haemoglobin conc.* | *Mortality* | *Cardiac failure* |
|---|---|---|---|---|
| Primary repair | 16 | <16 g/dl | 0 | 1 (6·3%) |
| | 17 | 16–19 g/dl | 2 (11·8%) | 7 (41·7%) |
| | 14 | >19 g/dl | 4 (28·6%) | 7 (50·0%) |
| | | | P>0·2 | P<0 05 |
| Previous shunt | 23 | | 0 | 0 |
| | 17 | | 1 (5·9%) | 1 (5·9%) |
| | 9 | | 1 (11 1%) | 2 (22 2%) |
| | | | NS | NS |
| All cases | 39 | <16 g/dl | 0 | 1 (2 6%) |
| | 34 | 16–19 g/dl | 3 (8·8%) | 8 (23·5%) |
| | 23 | >19 g/dl | 5 (21·7%) | 9 (39·1%) |
| | | | P<0 025 | P<0 001 |

TABLE 8 *Mortality and morbidity in relation to polycythaemia plus a prior shunt*

| *Category* | *Cases* | *Mortality* | *Low output cardiac failure* |
|---|---|---|---|
| Hb<16g/dl Shunted and unshunted | 38 | 0 | 1 (2·6%) |
| Hb>16 g/dl and shunted | 26 | 2 (7·7%) | 3 (11·5%) |
| Hb>16 g/dl and unshunted | 32 | 6 (18 6%) | 14 (43·8%) |
| | | P<0·0005 | P<0·0005 |

## Intraoperative correlates of postoperative mortality and morbidity

As indicated above, all the operations were conducted along substantially the same lines, and two

TABLE 9 *Mortality and morbidity in relation to polycythaemia, age, and prior shunting*

| *Category* | *Cases* | *Mortality* | *Low output cardiac failure* |
|---|---|---|---|
| Hb<16 g/dl Age>5 yr | 30 | 0 | 0 |
| Hb<16 g/dl Age<5 yr | 8 | 0 | 1 (12·5%) |
| Hb>16 g/dl Shunted Age>5 yr | 21 | 1 (5%) | 2 (10%) |
| Hb>16 g/dl Shunted Age<5 yr | 5 | 1 (20%) | 1 (20%) |
| Hb>16 g/dl Unshunted Age>5 yr | 20 | 3 (15%) | 7 (35%) |
| Hb>16 g/dl Unshunted Age<5 yr | 12 | 3 (25%) | 7 (58%) |

intraoperative factors were tested for correlation with the postoperative results. These were: (1) the relation of the right ventricular to the left ventricular systolic pressure at the completion of the operation, and (2) the method of right ventricular outflow tract reconstruction.

**Relation of ratio of right to left ventricular post repair systolic pressures to results of complete repair** At the conclusion of each operation, after cardiopulmonary bypass had been discontinued and when a reasonably stable circulation had been re-established, pressures were recorded in both the right and the left ventricular cavities by needle puncture. A ratio of right to left ventricular systolic pressures below one-third was regarded as indicating a good right ventricular outflow tract reconstruction. If the ratio was between one-third and two-thirds this was generally considered as acceptable but not optimal. If the ratio was in excess of two-thirds this was regarded as unsatisfactory, and on several occasions a further bypass run was conducted in an attempt to allow a more complete relief of the right ventricular outflow tract obstruction. The justification for these attitudes is apparent from perusal of Table 10 which shows quite clearly that there was a statistically significant increase in mortality and morbidity in those cases in which the right ventricular pressure remained high at the end of the repair operation. Shunted and unshunted cases were randomly distributed between the first two groups but as it happened a majority of cases in the third group had previously been shunted. The reason for this was, in part, that this group of patients had been regarded at the time of the original investigation to have a right ventricular outflow tract which was unfavourable for early repair, and hence some of these were shunted as a preliminary procedure hoping that as the child grew older right ventricular outflow tract reconstruction might be technically easier. Despite the fact that in general a previous shunt was associated with a low mortality and morbidity it does not seem to protect the patient from the serious prognostic import of a high residual right ventricular pressure.

TABLE 10 *Relation of RVp/LVp after repair to mortality and low output cardiac failure*

| *RVp/LVp* | *Cases* | *Mortality* | *Cardiac failure* |
|---|---|---|---|
| 0·40 | 34 | 1 (2·9%) | 4 (12 6%) |
| 0·40–0·70 | 51 | 3 (6·0%) | 9 (17·7%) |
| 0·70 | 11 | 4 (36·4%) | 5 (45·5%) |
| | | 0·005>P>0·001 | 0 01>P>0·05 |

Shunted and unshunted cases were randomly distributed between first 2 groups but 75 per cent of cases in third group were unshunted.
RVp/LVp=ratio of right to left ventricular systolic pressures.

**Method of right ventricular outflow tract reconstruction and results of total repair** While it is generally recognized that the major obstacle to successful total correction is difficulty with the reconstruction of the right ventricular outflow tract, it has none the less been suggested that a long outflow tract patch across the pulmonary valve ring resulting in pulmonary valve regurgitation is associated with higher mortality and morbidity and, therefore, should be avoided if at all possible (Kirklin and Karp, 1970). Our experience in this regard is set out in Table 11. Our patients were about equally divided into a first group with an intact, unobstructed pulmonary valve, a second group which required pulmonary valvotomy with the inevitable production of some pulmonary valve regurgitation, and a third group which required extensive patch reconstruction of the outflow tract with the patch extending across the pulmonary valve ring and therefore associated with free pulmonary valve regurgitation (except for three isolated cases in which a monocusp valve was constructed from pericardium). As can be seen, there was an increased mortality and morbidity in those patients requiring extensive right ventricular outflow tract reconstruction, but on the basis of these figures the observed difference was not significant. Our experience suggests that it is far more important to achieve more or less complete relief of right ventricular outflow tract obstruction by whatever means is necessary even if this leaves a regurgitant pulmon-

TABLE 11 *Relation of right ventricular outflow tract reconstruction to mortality and low output cardiac failure*

| *Reconstruction* | *Cases* | *Mortality* | *Cardiac failure* |
|---|---|---|---|
| Infundibulectomy alone | 30 | 1 (3·3%) | 3 (10%) |
| Infundibular patch | 5 | 0 | 0 |
| Pulmonary valvotomy with PR | 32 | 2 (6·25%) | 7 (21 9%) |
| Patch reconstruction across pulmonary valve ring | 29 | 5 (17·4%) | 8 (27·6%) |
| | | 0·30>P>0·20 | |

Shunted and unshunted cases appeared randomly distributed between 4 reconstruction groups.
PR=Pulmonary valve regurgitation.

ary valve. This last feature seems of little importance, in the short term at least, so long as the right ventricular pressure is low.

### Bypass time

Not surprisingly the total cardiopulmonary bypass time in the previously shunted group of patients was slightly longer than in the unshunted patients. The median bypass time for the shunted patients was 101 minutes compared with a median figure of 93 minutes for the unshunted patients, but this difference was not statistically significant from our figures.

### Postoperative drainage

Again, not surprisingly, the postoperative chest drainage during the first 6 hours in the previously shunted group was slightly larger, amounting to a median figure of 2·7 ml/kg$^{-1}$ hr$^{-1}$ compared with a median figure of 1·9 ml/kg$^{-1}$ hr$^{-1}$ for the unshunted group, but once again this difference was not statistically significant.

## Discussion

Although in the experience of some surgeons a previous systemic to pulmonary artery anastomosis is associated with a higher surgical mortality at the second stage repair (Ehrenhaft, Fisher, and Lawrence, 1963), the general consensus is that a previous shunt does not militate against a good result at the time of complete repair. There have been only a few published reports (Leachman, Hallman, and Cooley, 1965; Ebert and Sabiston, 1967) in which data are supplied to support the thesis that there is a lower incidence of complications in the previously shunted group. Two reasons have been advanced for this lower morbidity. In the first place a previous shunt results in a reduced haemoglobin level, and in the second place it may increase left ventricular size and work potential when this is initially small. Our data could be interpreted to support either or both of these hypotheses.

Early complete repair has been advocated (Barratt-Boyes and Neutze, 1973; Rees and Starr, 1973) because of the alleged high mortality from shunting in infancy. However, this has not been our experience. During the period in which we undertook the 96 total repairs which have been reviewed, we also operated on a further 37 infants, under the age of 2, with the tetralogy of Fallot and electively performed shunt operations, with only 2 hospital deaths (5·4%) and no late deaths. Only a few of this group of infants came forward for complete repair during the period under review. The number who died from natural causes without surgical referral is not known.

Clearly, the final answer to the question of the best surgical policy to follow in respect of these patients will come when it is possible to follow a whole cohort of infants with this diagnosis from infancy to adult life in centres with varying surgical policies. Only then will we be able truly to appreciate the total attrition from natural causes, from early shunting or early repair, and from early shunting (if indicated) and subsequent repair.

In the meantime, we believe our experience justifies a continuing policy (in our unit, at least) of performing a shunt procedure in infants with the tetralogy of Fallot who have significant hypoxic symptoms, especially if the right ventricular outflow tract, as depicted by cineangiography, seems to require an extensive reconstruction. Delayed, elective, total repair can then be undertaken with the expectation of a low operative mortality and morbidity.

Finally, our experience also lends strong support to the idea that persistent right ventricular hypertension after repair carries a bad immediate prognosis.

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# Results of total correction of the tetralogy of Fallot

## *Long-term haemodynamic evaluation at rest and during exercise*

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*Postoperative haemodynamic evaluation was performed on 15 patients 7 to 14 years (mean, 11 years) after total intracardiac repair of Fallot's tetralogy. The average age of the patients at the time of postoperative catheterization was 20 years (range 12 to 29) and they were all asymptomatic. Before operation 11 patients were severely cyanosed and disabled and 4 had mild cyanosis with anoxic spells.*

*The cardiac output and right heart pressures were measured at rest and after 5 minutes of submaximal exercise on a bicycle ergometer. It was shown that the degree of residual obstruction of the pulmonary outflow tract was slight and that the right ventricular/pulmonary arterial systolic gradient (RV/PA gradient) exceeded 20 mmHg (2·6 kPa) at rest in only 3 patients. The mean cardiac index at rest was 5·4 l $min^{-1}$ $m^{-2}$ which increased to 8·3 l $min^{-1}$ $m^{-2}$ during exercise. The response of the cardiac output during exercise was either normal or supranormal in 14 of the 15 patients. In the remaining patient the response was marginally below the normal range.*

*Pulmonary valvular regurgitation was present in 8 patients but there was no detectable difference in the cardiac function of these patients compared with patients with competent pulmonary valves.*

*Six of the patients investigated had also had cardiac catheterizations performed 1 to 4 years after operation. The results of the present study show that remarkably little change has occurred in their haemodynamic status in the intervening years. Though these results are encouraging, further studies are required to determine the eventual outcome of the RV pressure and volume overload.*

Total intracardiac correction of the tetralogy of Fallot is now well established as a highly successful surgical procedure (Kirklin and Karp, 1970). The symptomatic and clinical improvement which occurs after operation is usually dramatic. It is not surprising, however, that residual haemodynamic abnormalities have been shown by postoperative catheterization studies (Hallidie-Smith *et al.*, 1967; Soulié *et al.*, 1971; Sunderland *et al.*, 1973; Kaplan *et al.*, 1973; Gersony *et al.*, 1973).

Two main abnormalities have been described:

(1) Residual obstruction of the right ventricular outflow tract which is usually mild or moderate in degree.

(2) Pulmonary valvular regurgitation, particularly when a prosthetic or pericardial patch is used to enlarge the right ventricular outflow tract and the pulmonary artery.

In a minority of patients the persistence of a shunt through a ventricular septal defect has been shown.

Many of the postoperative studies were done relatively soon after total correction and there is an

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obvious need to determine the long-term effects of the residual haemodynamic defects. In addition, the majority of follow-up catheterizations did not examine the effects of exercise on the right ventricular outflow tract gradient and the cardiac output. The haemodynamic response to submaximal exercise in the supine position has been reported (Malm *et al.*, 1966; Gotsman, 1966; Bristow *et al.*, 1970; Joransen and Moller, 1972; Shah and Kidd, 1966) and intense exercise in the upright position has been the subject of one report (Epstein *et al.*, 1973).

The present studies were undertaken to evaluate the long-term haemodynamic results at rest and during exercise in 15 patients approximately 11 years after total correction. It was also possible to make an assessment of the serial haemodynamic changes in 6 patients who had been studied 1 to 4 years after operation (Gotsman, 1966).

## Patients and methods

Fifteen patients, 8 male and 7 female, were investigated 7 to 14 years after total correction of Fallot's tetralogy, and in 11 patients the interval was greater than 10 years. Their average age at the time of investigation was 20 years (range 12 to 29 years) and they were all asymptomatic and leading normal lives. They were selected because they were the earliest survivors of the total correction operation in our unit. The purpose and nature of the investigation was fully explained to each patient or patients as appropriate and informed consent for its performance obtained.

Before operation 11 patients were severely cyanosed and 4 had mild cyanosis with anoxic spells. The diagnosis was based on the clinical signs, haemodynamic and angiographic investigation, and the findings were confirmed at operation.

### Operation details

Five patients had preliminary palliative operations, viz. a pulmonary valvotomy in 3 and a Blalock anastomosis in 2. At the time of total correction pulmonary infundibulectomy was done in all 15 patients and in addition 8 patients had a pulmonary valvotomy. The ventricular septal defect was repaired with a 'teflon' patch in 9 patients and in the other 6 patients the defect was closed by direct suture. The right ventricular outflow tract was widened with a 'teflon' prosthetic patch in 7 patients and in 2 of these the prosthetic patch was extended to widen the proximal pulmonary artery.

### Procedure for cardiac catheterization

Right heart catheterization was performed in the supine position and in the fasting state without earlier sedation. A No. 9 double-lumen Cournand catheter was used in most studies and the intracardiac pressures were measured by Sanborn transducers (Model 267 BC) and recorded on an ultraviolet photographic recorder. The pulmonary arterial and right ventricular pressures were determined by planimetry over several respiratory cycles. The right ventricular end-diastolic pressure (RVEDP) was measured after the 'a' wave. The zero reference level for pressure was 10 cm above the plane of the catheterization table. The oxygen saturation of blood samples from the superior vena cava, inferior vena cava, right atrium, right ventricle, pulmonary artery, and brachial artery was determined by a spectrophotometric method. The cardiac output was measured by the direct Fick method. The expired air was collected in a Tissot spirometer while samples of blood were withdrawn from the pulmonary artery and brachial artery

TABLE 1 *Postoperative data in 15 patients with tetralogy of Fallot*

| | *Rest* *Mean* | *Range* | *Exercise* *Mean* | *Range* |
|---|---|---|---|---|
| Mean RAP (mmHg) | 5 | −1–10 | 7 | 1–10 |
| RVSP (mmHg) | 39 | 22–61 | 54 | 23–83 |
| RVEDP (mmHg) | 6 | 0–13 | 7 | −2–12 |
| PASP (mmHg) | 24 | 14–36 | 33 | 18–49 |
| PADP (mmHg) | 8 | −1–18 | 13 | 5–22 |
| Mean PAP (mmHg) | 15 | 6–26 | 22 | 8–33 |
| RV/PA systolic pressure gradient (mmHg) | 15 | 1–46 | 23 | 3–59 |
| PAWP (mmHg) | 8 | 0–19 | 13 | 4–30 |
| BA systolic (mmHg) | 128 | 99–150 | 160 | 120–181 |
| BA diastolic (mmHg) | 84 | 67–102 | 101 | 72–119 |
| PVR (dynes·s·cm$^{-5}$) | 87 | 36–175 | 65 | 11–141 |
| Systemic resistance (dynes·s·cm$^{-5}$) | 1080 | 508–1724 | 956 | 487–899 |
| Systemic arterial oxygen saturation (%) | 95 | 88–99 | 95 | 86–98 |
| AV oxygen difference (vol %) | 3·3 | 2 1–4 8 | 8 0 | 5 4–11·3 |
| Cardiac index (l min$^{-1}$ m$^{-2}$) | 5·4 | 3·2–8·5 | 8·3 | 5·1–11·8 |
| Heart rate (beats/min) | 88 | 72–108 | 135 | 108–166 |
| Stroke volume (ml/beat) | 96 | 62–185 | 100 | 61–173 |
| Oxygen consumption (ml min$^{-1}$ m$^{-2}$) | 153 | 113–192 | 597 | 444–755 |

*Abbreviations:* RAP, right atrial pressure; RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; BA, brachial artery; PVR, pulmonary vascular resistance; AV, arteriovenous.

*Conversion factors from Traditional Units to SI Units;* 1 mmHg≈0·133 kPa; 10 dynes·s·cm$^{-5}$=1 MPa·s·m$^{-3}$.

simultaneously. The gas samples were analysed for oxygen content by the Scholander micro-method. The cardiac output was measured at rest and during the fifth minute of exercise on a bicycle ergometer. The degree of workload selected for each patient was approximately two-thirds of the predetermined maximum load and it was maintained for 5 minutes. Simultaneous pulmonary arterial (PA) and right ventricular (RV) pressures were recorded at the beginning and at the end of the gas collection.

### Electrocardiography

All the patients had complete right bundle-branch block on their electrocardiograms but there was no evidence of left anterior hemiblock or complete atrioventricular dissociation.

## Results

The physical characteristics of the patients and haemodynamic results at rest and during exercise are shown in Tables 1 and 2.

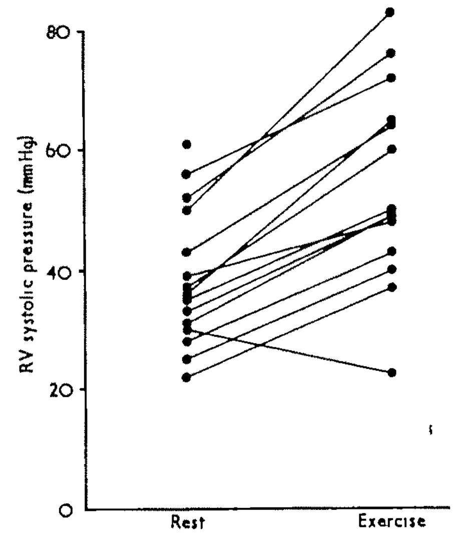

FIG. 1 *Right ventricular systolic pressures at rest and during exercise.*

### Right heart pressures

The mean values for the RV systolic pressure and the RV-PA systolic pressure gradient at rest and during exercise are given in Table 1 and the individual values are shown in Fig. 1 and 2. The RV-PA systolic gradient at rest was 20 mmHg (2·7 kPa) or less in 12 of the 15 patients. An increase in the gradient during exercise was recorded in 14 patients but the increase was < 10 mmHg (1·3 kPa) in 7 patients. The RV-LV peak pressure ratio averaged 0·31 (range 0·16 to 0·42) and there was no significant difference between the patients who had a patch repair of the RV outflow tract and those who did not.

The RVEDP was slightly increased ( >5 mmHg; 0·7 kPa) in 10 patients at rest (Fig. 3). During exercise the RVEDP increased in 10 patients but the increase exceeded 5 mmHg (0·7 kPa) in only 1 patient.

The mean pulmonary artery pressure (PAP) and pulmonary wedge pressures (PAWP) were within

TABLE 2 *Physical characteristics and values for cardiac output, cardiac index, AV $O_2$ difference, and oxygen consumption at rest and during exercise*

| *Case No.* | *Age* | *Sex* | *BSA ($m^2$)* | *AV $O_2$ Differences (vol %)* | | *Cardiac output (l/min)* | | *Cardiac index (l $min^{-1}$ $m^{-2}$)* | | *Oxygen consumption index (ml $min^{-1}$ $m^{-2}$)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Rest* | *Exercise* | *Rest* | *Exercise* | *Rest* | *Exercise* | *Rest* | *Exercise* |
| 1 | 21 | M | 1·69 | 3·8 | 8·9 | 6·4 | 13·6 | 3·8 | 8·0 | 143 | 714 |
| 2 | 24 | F | 1·49 | 2·3 | 6·7 | 10·6 | 9·9 | 7·1 | 6·6 | 166 | 444 |
| 3 | 23 | M | 1·94 | 4·0 | 10·7 | 7·3 | 13·3 | 3·7 | 6·9 | 148 | 731 |
| 4 | 23 | F | 1·59 | 2·7 | 5·0 | 6·7 | 15·0 | 4·2 | 9·3 | 113 | 465 |
| 5 | 12 | F | 1·44 | 2·3 | 5·7 | 9·7 | 12·7 | 6·8 | 8·8 | 155 | 500 |
| 6 | 17 | M | 1·63 | 2·3 | 6·2 | 13·4 | 15·3 | 8·5 | 9·4 | 192 | 585 |
| 7 | 17 | M | 1·72 | 3·9 | 6·8 | 6·9 | 14·0 | 4·0 | 8·2 | 158 | 552 |
| 8 | 19 | M | 1·81 | 3·8 | 10·9 | 6·5 | 11·7 | 3·6 | 6·5 | 138 | 703 |
| 9 | 14 | M | 1·30 | 3·8 | 6·4 | 5·8 | 15·4 | 4·5 | 11·8 | 172 | 755 |
| 10 | 29 | F | 1·64 | 2·4 | 6·5 | 10·6 | 14·2 | 6·4 | 8·6 | 153 | 561 |
| 11 | 18 | F | 1·54 | 3·2 | 8·5 | 6·5 | 10·0 | 4·3 | 6·5 | 137 | 557 |
| 12 | 17 | F | 1·71 | 2·6 | 7·1 | 10·6 | 15·1 | 6·2 | 8·8 | 163 | 621 |
| 13 | 24 | M | 1·60 | 4·8 | 11·3 | 5·5 | 8·2 | 3·4 | 5·1 | 164 | 579 |
| 14 | 17 | M | 1·78 | 2·1 | 5·4 | 15·0 | 18·7 | 8·4 | 10·5 | 180 | 566 |
| 15 | 25 | F | 1·63 | 3·6 | 10·0 | 5·2 | 10·2 | 3·2 | 6·3 | 116 | 625 |

*Normal values at rest:* (1) AV oxygen difference, 2·4 to 5·7 vol. %; (2) cardiac index, 2·6 to 5·8 l $min^{-1}$ $m^{-2}$; (3) oxygen consumption index, 110 to 192 ml $min^{-1}m^{-2}$. Fuller details are given in a paper by Segeal *et al.* (1964).

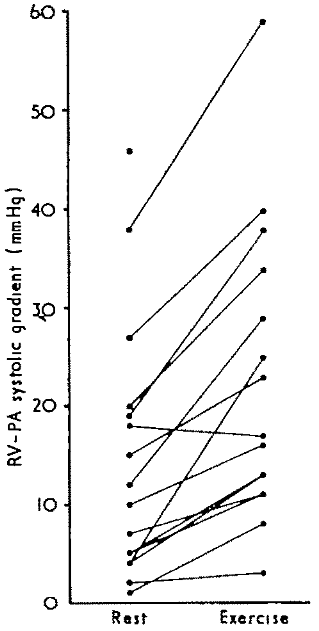

FIG. 2 *Right ventricular-pulmonary arterial systolic pressure gradient at rest and during exercise.*

normal limits at rest in all except one patient in whom the PAWP was 19 mmHg (2·5 kPa). The mean pulmonary vascular resistance was also normal at rest and it decreased during exercise.

### Cardiac index (Table 2)

The mean cardiac index at rest was $5{\cdot}4 \pm 1{\cdot}9$ l min$^{-1}$ m$^{-2}$ and was above the normal range for this laboratory (2·6 to 5·8 l min$^{-1}$ m$^{-2}$) in 6 patients. The relation between cardiac index and oxygen uptake during exercise was below normal in only 1 patient (Fig. 4).

At rest the mean AV oxygen difference and oxygen uptake were within the normal range. During exercise the mean oxygen uptake increased almost fourfold and the mean AV oxygen difference more than doubled. The values for 6 subjects were less than those for normal subjects doing a comparable level of exercise (Donald *et al.,* 1955). The relation between the AV oxygen difference and the oxygen uptake for individuals is shown in Fig. 5.

### Stroke volume

The stroke volume increased in 8 patients during exercise and decreased in 7; the changes were generally small (Fig. 6).

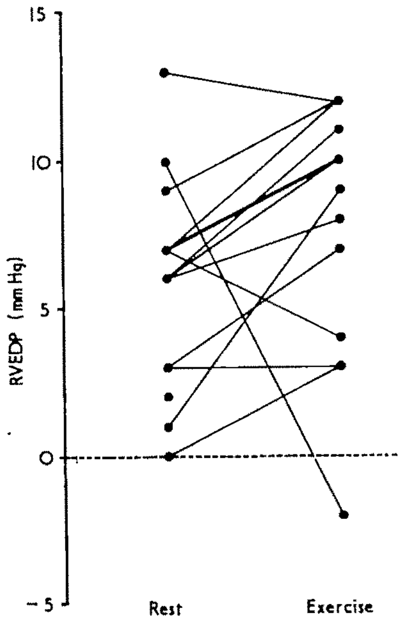

FIG. 3 *Right ventricular end-diastolic pressures at rest and during exercise.*

### Relation between stroke index and RVEDP during exercise (Fig. 7)

The stroke index increased during exercise in 7 patients and this increase was accompanied by a rise in RVEDP in 5 patients. However, the increase in RVEDP did not exceed 5 mmHg (0·7 kPa). A

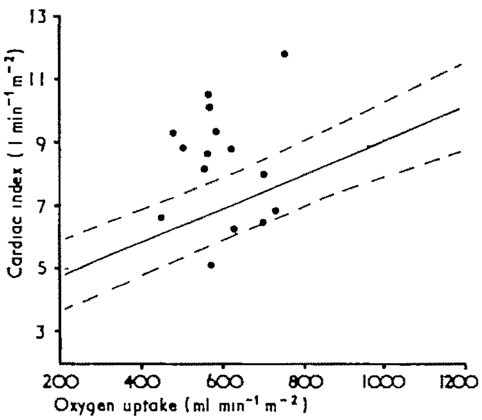

FIG. 4 *Relation between cardiac index and oxygen uptake during exercise. The normal regression line and 95 per cent confidence limits are shown (Donalp* et al., *1955).*

substantial fall in stroke index was observed in 2 patients and in 1 of these the RVEDP remained unchanged while in the other the RVEDP increased by 4 mmHg (0·5 kPa). In one further patient the stroke index fell by 8 ml $\text{min}^{-1}\,\text{m}^{-2}$ while the RVEDP increased from 1 mmHg (0·1 kPa) to 9 mmHg (1·2 kPa).

## Oxygen saturations

The mean arterial oxygen saturation at rest and during exercise was identical (95 ±3 per cent). Two patients showed a significant reduction of the arterial saturation at rest (90 and 88%). In one of these patients an increase occurred during exercise from 90 to 93 per cent but a further reduction to 86 per cent was observed in the other patient.

Analysis of the right heart blood samples by spectrophotometer revealed no evidence of a left-to-right shunt.

## Effects of pulmonary regurgitation

Eight patients had early diastolic murmurs in the pulmonary area and these showed haemodynamic evidence of pulmonary regurgitation (pulmonary artery diastolic pressure within 0 to 2 mmHg (0 to 0·3 kPa) of the RVEDP).

In patients without pulmonary regurgitation the mean RVEDP at rest was 6 mmHg (0·8 kPa) and it was unchanged during exercise. The mean RVEDP at rest was also 6 mmHg (0·8 kPa) in the patients with pulmonary regurgitation and exercise caused a slight increase to 9 mmHg (1·2 kPa). The highest individual value recorded at rest was 13 mmHg (1·7 kPa) in a patient with pulmonary regurgitation (Fig. 3).

The mean pulmonary artery pulse pressure was 19 ±6 mmHg (2·5 ±0·8 kPa) in the patients with pulmonary regurgitation compared to 13 ±5 mmHg (1·7 ±0·7 kPa) in those without pulmonary regurgi-

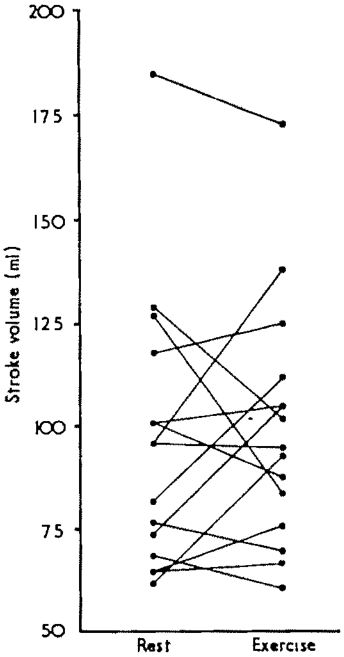

FIG. 6 *The stroke volume for individual patients at rest and the changes occurring during exercise.*

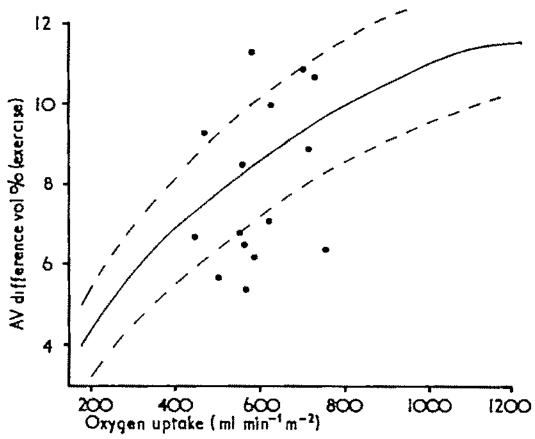

FIG. 5 *Relation between AV oxygen difference and oxygen uptake during exercise. The normal regression line and 95 per cent confidence limits are shown (Donald* et al., *1955).*

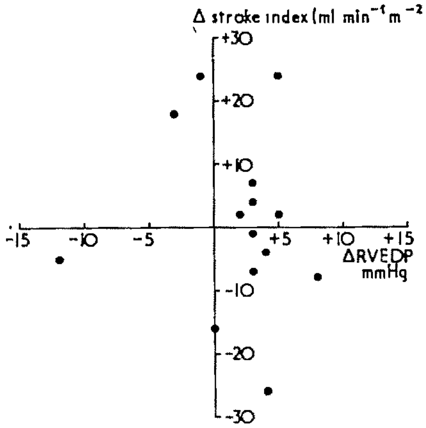

FIG. 7 *Changes in stroke index and right ventricular end-diastolic pressure during exercise.*

TABLE 3 *Comparison of early and late haemodynamic results at rest in 6 patients*

| *Case No.* | *RVSP (mmHg)* | | *RV/PA systolic gradient (mmHg)* | | *RVEDP (mmHg)* | | *RAP (mmHg)* | | *PASP (mmHg)* | | *PADP (mmHg)* | | *PAWP (mmHg)* | | *Cardiac index ($l\,min^{-1}\,m^{-2}$)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* | *Early* | *Late* |
| 2 | 31 | 25 | 1 | 5 | 7 | 3 | 5 | −1 | 30 | 20 | 6 | −1 | 8 | 2 | 3·9 | 7·1 |
| 7 | 60 | 50 | 35 | 19 | 5 | 7 | 5 | 4 | 25 | 31 | 6 | 8 | 4 | 10 | 3·4 | 4·0 |
| 8 | 30 | 36 | 14 | 12 | 7 | 6 | 8 | 8 | 16 | 24 | 8 | 10 | 7 | 2 | 2·4 | 3·6 |
| 9 | 25 | 35 | 7 | 10 | 6 | 13 | 6 | 10 | 18 | 25 | 8 | 13 | 10 | 15 | 4·7 | 4·5 |
| 10 | 43 | 39 | 16 | 18 | 6 | 1 | 5 | 5 | 27 | 21 | 9 | 9 | 10 | 9 | 3·9 | 6·4 |
| 15 | 31 | 37 | 5 | 7 | 7 | 7 | 7 | 8 | 30 | 30 | 8 | 6 | 7 | 19 | 4·5 | 3·2 |
| Mean | 37 | 37 | 13 | 12 | 6 | 6 | 6 | 6 | 24 | 25 | 8 | 8 | 8 | 10 | 3·8 | 4·8 |
| SD | ±13 | ±8 | ±12 | ±5 | ±1 | ±4 | ±1 | ± 4 | ±6 | ±5 | ±1 | ±5 | ±2 | ±7 | ±0·8 | ±1·6 |

*Abbreviations:* as for Table 1.

tation; this difference is not statistically significant ($P > 0{\cdot}05$). Minor differences in the cardiac output were observed in the two groups at rest and on exercise. The mean cardiac index at rest in patients with pulmonary regurgitation was 6·1 $l\,min^{-1}\,m^{-2}$ increasing to 9·0 $l\,min^{-1}\,m^{-2}$ on exercise compared to 4·6 $l\,min^{-1}\,m^{-2}$ increasing to 7·6 $l\,min^{-1}\,m^{-2}$. These differences were not statistically significant ($P > 0{\cdot}1$ rest; $P > 0{\cdot}05$ exercise).

## Comparison of serial haemodynamic results

The results of the early and late postoperative catheterization studies are compared in Table 3 and they show remarkably little change in the intervening years. The mean RV systolic pressure, RVEDP, RAP, and PA diastolic pressures are identical and there are only minor changes in the RV-PA gradient, PA systolic, PA mean, and PAWP. However, one patient showed a significant increase in the PAWP from 7 to 19 mmHg (0·9 to 2·5 kPa) at rest and from 14 to 30 mmHg (1·9 to 4·0 kPa) during exercise. The effects of exercise were measured in only 3 patients who showed no significant haemodynamic change between the two studies.

The mean cardiac index in the early study was 3·8 ±0·8 $l\,min^{-1}\,m^{-2}$ compared to 4·8 ±1·6 $l\,min^{-1}\,m^{-2}$ in the later study. The difference is not statistically significant ($P > 0{\cdot}1$). The mean AV oxygen difference at rest in both studies was within the normal range and only 1 patient had a value significantly greater than normal during exercise.

## Discussion

The majority of haemodynamic studies after total correction for Fallot's tetralogy have shown a decrease in the RV/PA systolic pressure gradient in later studies compared with measurements made immediately after operation (Kirklin and Karp, 1970; Muraoka *et al.*, 1973). The results of catheterizations performed 5 to 6 years postoperatively compared with 1 year after operation have shown little subsequent haemodynamic change (Gotsman *et al.*, 1969; Bristow *et al.*, 1970). The RV/LV ratio was selected by Hawe *et al.* (1972) as the most valid indicator of the degree of pulmonary stenosis. They studied 37 patients and showed in 25 patients that the RV/LV ratio decreased between the completion of repair and restudy by 10 to 53 per cent. The ratio was unchanged in 4 patients and in 8 it was increased by 10 to 73 per cent.

In our study the RV/LV peak pressure ratio was 0·31 (range 0·16 to 0·42) and this indicates satisfactory relief of the pulmonary stenosis. It was also noted that the ratio did not differ significantly between patients who had a prosthetic patch in the right ventricular outflow tract and those who did not. Exercise caused an increase in the RV/PA systolic pressure gradient but the increase was slight or trivial in the majority of patients though more intense exercise would probably have shown a further increase (Epstein *et al.*, 1973). Nevertheless, the increase in pulmonary blood flow during exercise was well tolerated. Another important observation was the unchanged RV/PA systolic pressure gradient in the patients catheterized previously. The relatively small increase in the RV/PA gradient during exercise and the constancy of the haemodynamic measurements with the passage of time strongly suggests that the restoration of a normal pulmonary blood flow provides an adequate stimulus for the growth of the right ventricular outflow tract and the pulmonary arteries.

## Right ventricular myocardial function

The RVEDP was greater than 5 mmHg (0·7 kPa) in 10 patients and instead of the normal fall during exercise the RVEDP showed a further slight increase. Pulmonary regurgitation is one possible reason for the increased RVEDP but diminished right ventricular compliance caused by persisting muscular hypertrophy or myocardial fibrosis may also be important. A fall in the stroke volume index and a concomitant increase in the RVEDP during exercise has been interpreted as indicating abnormal right ventricular myocardial function in patients with Fallot's tetralogy after total correction (Joransen and Moller, 1972) and also after pulmonary valvotomy for pulmonary stenosis (Finnegan *et al.*, 1974; Stone *et al.*, 1974). A similar occurrence was observed in 5 patients in the present study. Because of the presence of pulmonary regurgitation and the brevity of the isovolumic period in the right ventricle, it was not possible to derive indices of myocardial contractility (Vmax, Vpm) and therefore a more direct assessment of myocardial contractile function was not made.

### Pulmonary hypertension

An increase in the pulmonary vascular resistance has been observed in the early postoperative period in the majority of patients (Albertal, Swan, and Kirklin, 1964) and in some patients thereafter (Lillehei *et al.*, 1964; Hallidie-Smith *et al.*, 1967; Gersony *et al.*, 1973; Kinsley *et al.*, 1974). However, other studies have shown a normal pulmonary vascular resistance and mean pulmonary artery pressures (Gotsman, 1966; Bristow *et al.*, 1970; Epstein *et al.*, 1973; Shah and Kidd, 1966). In our study there was no evidence of pulmonary arterial hypertension at rest or during exercise. The fall in the pulmonary vascular resistance during exercise shows the ability of the pulmonary vascular system to accommodate the increased pulmonary blood flow. This finding lends support to the view that the thrombotic lesions, seen in the pulmonary arteries of cyanotic patients, usually resolve when the pulmonary blood flow increases (Ferencz, 1960).

### Pulmonary valvular regurgitation

The problem of pulmonary valvular regurgitation after total correction continues to cause concern as to its ultimate effects on right ventricular function. Though some authors consider pulmonary regurgitation to be the major postoperative problem (Soulié *et al.*, 1971), others have concluded that it appears to be well tolerated (Malm *et al.*, 1963; Gotsman, 1966; Jones *et al.*, 1973; Sunderland *et al.*, 1973).

In our study there was no significant difference in the resting cardiac output or the response to exercise in patients with and without pulmonary regurgitation. The slight increase in RVEDP during exercise was the main difference between the two groups. It appears, therefore, that pulmonary regurgitation is well tolerated but further observation is necessary to determine its ultimate significance because a long-term experimental study of pulmonary regurgitation has shown the development of right ventricular dilatation and hypertrophy and a reduced resting cardiac output (Ellison *et al.*, 1970).

### Recurrence of ventricular septal defect

Several authors report that the ventricular septal defect reopens in a small number of patients after total correction (Bristow *et al.*, 1970; Sunderland *et al.*, 1973; Joransen and Moller, 1972). Analysis of the right heart blood samples by spectrophotometer showed no evidence of left-to-right shunting in any of our patients. This does not exclude the presence of a small left-to-right shunt but more sensitive methods of shunt detection were not used by us.

### Systemic oxygen saturations

The arterial oxygen saturations were normal in all except 2 patients at rest. One patient had an oxygen saturation of 90 per cent which increased to 93 per cent during exercise. The other patient had an oxygen saturation of 88 per cent and a further decrease to 86 per cent occurred during exercise. This patient was asymptomatic and had a high resting cardiac output, a normal response of the cardiac output during exercise, and a trivial degree of right ventricular outflow tract obstruction (RV/PA systolic gradient at rest=5 mmHg (0·7 kPa)). The reason for the arterial unsaturation is, therefore, unexplained but it may be attributable to a persistent abnormality of pulmonary blood flow distribution.

### Left ventricular function

Abnormal left ventricular function has been reported before and after total correction of Fallot's tetralogy (Jarmakani *et al.*, 1972). The main abnormality described was a decreased left ventricular ejection fraction. Left ventricular function was not studied directly by us but the pulmonary wedge pressure was within normal limits in 14 patients. One patient had a PAWP at rest of 19 mmHg (2·5 kPa) which increased to 30 mmHg (4·0 kPa) during exercise. In the majority of patients, however, the failure to develop pulmonary hypertension and the response of the stroke volume during exercise probably indicates normality of LV function.

## Cardiac output

The mean resting cardiac index for the group was 5·4 l min$^{-1}$ m$^{-2}$ which is at the upper limit of normal and 6 patients had cardiac outputs above the normal range. Six subjects had a normal response of the cardiac output during exercise and 1 patient was slightly below the normal range. The remaining 8 patients had high cardiac outputs during exercise and this was associated with low AV oxygen differences. Though the patients were generally anxious there was no evidence of hyperventilation during the catheterization procedure or any other reason for the high output state such as anaemia, thyrotoxicosis, or arteriovenous shunting. However, the presence of small left-to-right shunts undetected by analysis of oxygen saturations is a possible explanation.

In normal subjects the response of the stroke volume during exercise is variable; it usually increases or is unaltered but it may fall (Donald *et al.*, 1955). In patients with pulmonary stenosis studied postoperatively, a similar variability was observed (Finnegan *et al.*, 1974; Stone *et al.*, 1974). Another study of patients with pulmonary stenosis showed that in the presence of mild stenosis the stroke volume increased on exercise but when the stenosis was more severe the stroke volume remained constant (Moller, Rao, and Lucas, 1972). In our study the changes in stroke volume during exercise were also variable. The stroke volume increased in 8 subjects and decreased in 7, though a substantial decrease was observed in only 2 patients (38 ml and 27 ml).

The response of the cardiac output during submaximal exercise testing is clearly very satisfactory, but testing during more intensive exercise has shown a consistently reduced response (Epstein *et al.*, 1973). Nevertheless, considering the presence of residual defects such as right ventricular outflow tract obstruction and pulmonary regurgitation, the performance of these patients during exercise is remarkably good. The ultimate effect of the residual abnormalities can only be determined by further clinical and haemodynamic studies.

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# Duplication of aortic wall seen by echocardiography

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*In four patients, echocardiography showed duplication of an aortic wall echo. An aortic dissection was present in only one. Other causes for the echocardiographic pattern were abscess in the interventricular septum, mitral stenosis, and dilatation of the noncoronary sinus of Valsalva. Division of the echo from the mitral ring into two separate posterior aortic wall echoes was seen only in the patient with dissecting aneurysm; it is suggested that this appearance adds to the specificity of the finding of aortic wall duplication by echocardiography in the diagnosis of aortic dissection.*

The echocardiogram has been shown to be useful in the diagnosis of dissecting aortic aneurysm involving the aortic root (Millward, Robinson, and Craige, 1972; Nanda, Gramiak, and Shah, 1973; Yuste *et al.,* 1974). Findings that suggest dissection are widening or duplication of one or both aortic walls (Millward *et al.,* 1972; Nanda *et al.,* 1973; Yuste *et al.,* 1974) and pronounced variation in aortic root diameter with minor changes in transducer angulation (Nanda *et al.,* 1973). These patterns may, however, be seen in conditions other than aortic dissection (Nanda *et al.,* 1973; Krueger *et al.,* 1975). We are reporting here echocardiograms from four patients which showed apparent duplication of one or both aortic walls. In one patient an aortic dissection was present. In the second there was no aortic dissection, but an abscess in the interventricular septum was found at necropsy. In the third, angiography showed aneurysmal dilatation of the aortic root and noncoronary sinus of Valsalva. In the fourth, reflection from the mitral ring produced an echo parallel with the posterior aortic wall echo.

## Methods

Echocardiograms were performed with a Picker EV 10 echocardiograph with a polaroid film or interfaced with a Honeywell 1856 strip chart recorder and with a Unirad echocardiograph used with a Tektronics strip chart recorder. A focused 2·25 MHz 1·3 cm transducer was used. Aortic root dimensions were measured from the centre of the anterior aortic wall echo to the centre of the posterior aortic wall echo at end-systole.

## Case reports

### Case 1

This 61-year-old woman had been admitted to hospital in September 1974, with a history of chest pain, shortness of breath, and syncope. A pulmonary arteriogram showed a large filling defect in the right pulmonary artery. She was treated initially with intravenous heparin, and was discharged on treatment with warfarin. In January 1975, a murmur of aortic regurgitation was noted. A chest *x*-ray film showed an increase in heart size.

On admission to San Francisco General Hospital on 11 March 1975, the blood pressure was 130/55 mmHg (17·3/7·3 kPa) in the left arm and 85/60 mmHg (11·3/8·0 kPa) in the right arm. The pulse was regular at 120 beats/min. The neck veins were not distended; râles were heard at both lung bases. The first heart sound was quiet; the aortic component of the second sound was accentuated; a third heart sound was present at the apex; there was a grade 3/6 systolic ejection murmur at the base and a grade 2/6 diastolic blowing murmur along the left sternal edge. The liver was not enlarged or tender. There was 2+ pitting oedema of the ankles. A chest *x*-ray film showed an enlarged cardiac silhouette, a wide mediastinum, and pulmonary venous congestion. The electrocardiogram showed changes of

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anterior wall infarction which had appeared since September 1974. A retrograde aortogram from the right femoral artery showed an aortic dissection, with opacification of both a true and a false lumen and demonstration of a re-entry point in the left external iliac artery. The catheter could not be passed above the lower abdominal aorta. The patient was transferred to the University of California Mcffitt Hospital for operation.

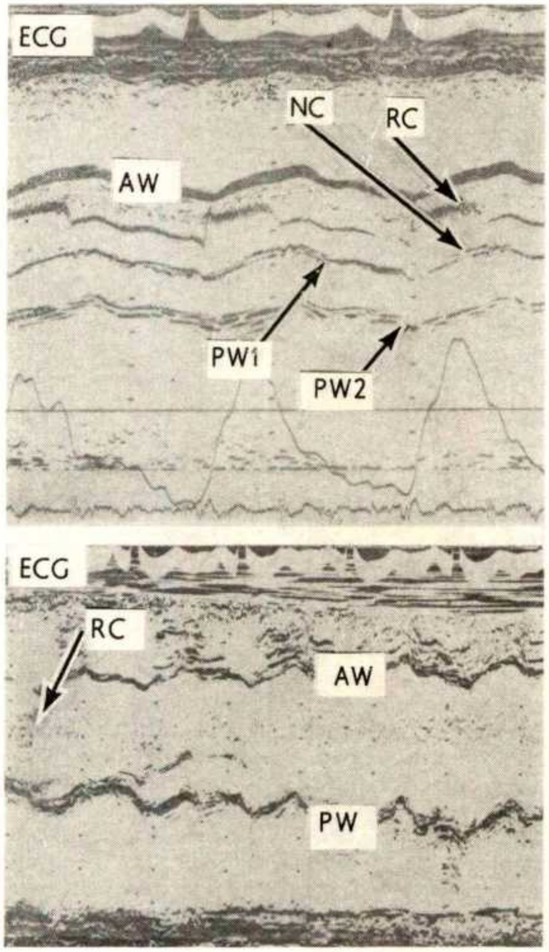

FIG. 1 *Echocardiograms in Case 1 before operation. (a) Duplication of posterior aortic wall echo (PW1 and PW2). Diameter of presumed aortic lumen (AW to PW1) is 25 mm; diameter of the presumed false lumen (PW1 to PW2) is 13 mm. (b) With slight cephalad redirection of transducer, aortic diameter increases from 34 to 46 mm. AW=anterior aortic wall; NC=noncoronary cusp; RC=right coronary cusp.*

Echocardiograms obtained then showed a thickened anterior aortic wall echo and duplication of the echo from the posterior aortic wall (Fig. 1a). The noncoronary cusp appeared to open only as far as the anterior component of the posterior aortic wall echo. A sweep of the aortic root cephalad from the level of the aortic valve (Fig. 1b) showed a marked increase in the diameter of the aorta with minor change in angulation of the transducer. The distance between the two posterior wall echoes varied with transducer position. In Fig. 1a, a 13 mm space is present; in Fig. 2a, the space is 7 mm. When the transducer is angled more laterally (Fig. 2b), only a single posterior aortic wall echo is imaged. A sweep from the mitral valve to the aortic root (Fig. 2c) showed the mitral ring echo to be in continuity with both posterior aortic wall echoes.

At operation, an aortic dissection was found to extend into the sinuses of Valsalva. The false lumen was widest over the right and noncoronary cusps. The left coronary artery was sheared off at its origin. Support of the aortic valve was restored by reattaching intima to adventitia at the valve ring. The aorta was replaced with a woven Dacron graft sewn immediately above the valve ring.

Fig. 3 shows an echocardiogram two weeks after operation. Duplication of the posterior aortic wall echo can no longer be seen.

### Case 2

A 35-year-old male user of illicit intravenous drugs was admitted to San Francisco General Hospital on 16 July 1973 with cellulitis on the right arm. No heart murmur was present then. Blood cultures grew *Staphylococcus epidermidis*. Intravenous administration of cephalothin (1 g every 6 hours) for one week resulted in resolution of the cellulitis; the patient then left the hospital against medical advice.

He was readmitted on 28 August 1973 with a 2-week history of fever, chills, arthralgia, fatigue, and anorexia. The blood pressure was 94/40 mmHg (12·5/5·3 kPa), the pulse regular at 110 beats/minute, and the temperature 38·6°C. The neck veins were not distended. The carotid arterial pulse was collapsing in quality. The lungs were clinically normal. Loud decrescendo diastolic and apical pansystolic murmurs were heard. Petechiae were present on the conjunctivae. Blood cultures grew *Serratia marcescens* and treatment was started with streptomycin intramuscularly (1 g every 12 hours). On the fifth day, the patient was transferred to the University of California Moffitt Hospital for evaluation for aortic valve replacement. Repeat blood cultures were positive for *Serratia*. On the

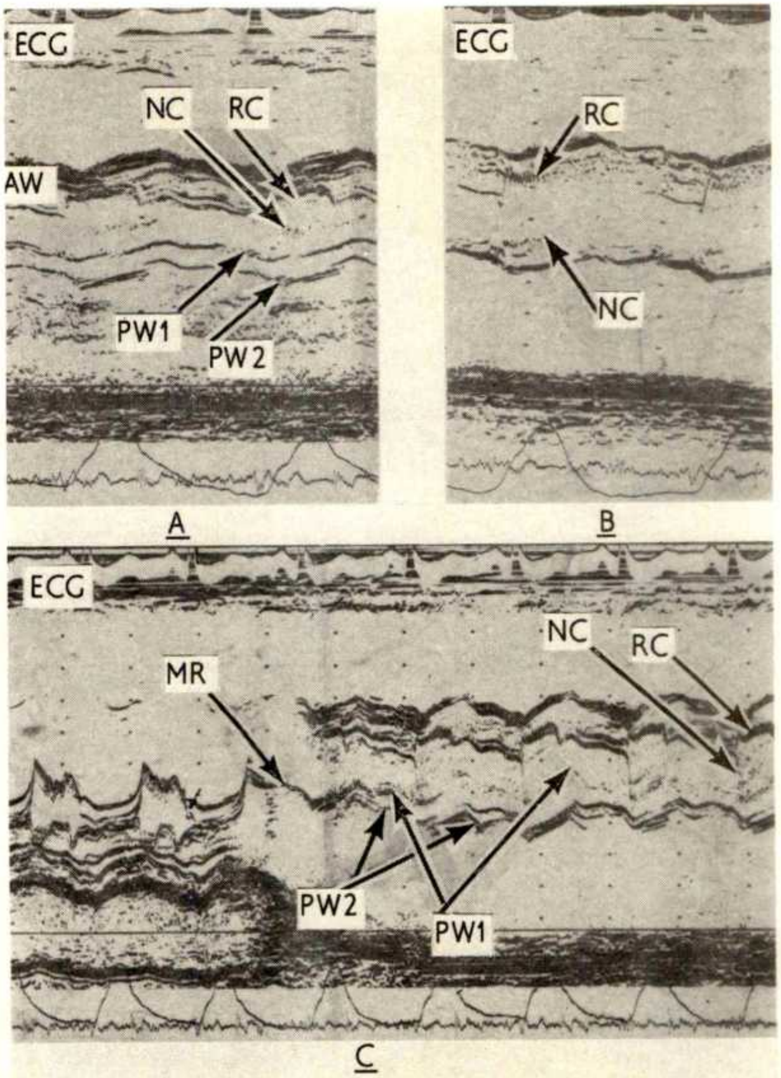

FIG. 2 *Echocardiograms in Case 1 before operation. (a) A 7 mm space is present between the two posterior aortic wall echoes (PW1 to PW2). (b) With transducer angled more laterally, a single posterior aortic wall echo is seen. The noncoronary aortic cusp is seen in systole to open nearly to the posterior wall. (c) Sweep from mitral valve to aortic root, showing two echoes from posterior aortic wall appearing to arise from echo of mitral ring (MR). See Fig. 1 for abbreviations.*

tenth day, râles developed and right bundle-branch block was noted on the electrocardiogram. An echocardiogram (Fig. 4a) showed duplication of the anterior aortic wall echo. Some views showed a cloud of echoes just posterior to the right coronary cusp during systole (Fig. 4b). In addition, prominent vibrations of the anterior mitral leaflet occurred during diastole and the mitral valve closed early. On the 13th day, heart failure worsened, complete heart block developed, and the patient died. No aortic dissection was found at necropsy, but a 30 mm vegetation was attached to the right coronary cusp, and an abscess was present high in the interventricular septum (Fig. 4b).

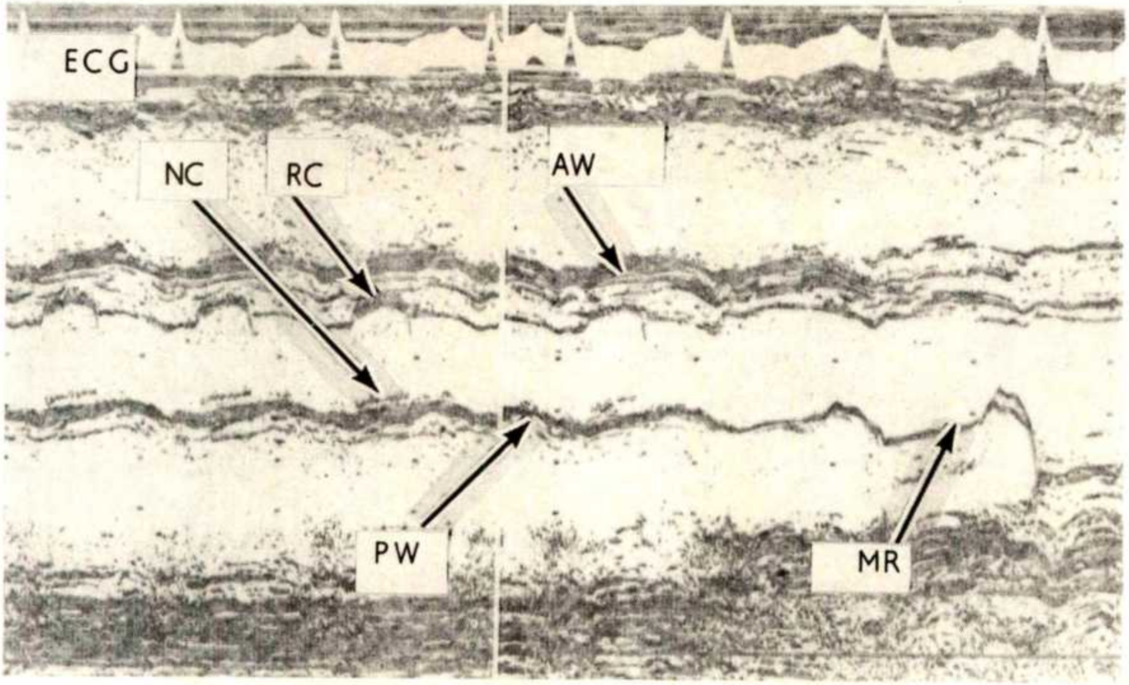

FIG. 3 *Echocardiogram in Case 1 after operation. Duplication of posterior aortic wall echo is no longer seen. See Fig. 1 and 2 for abbreviations.*

## Case 3

A 49-year-old man was admitted to San Francisco Veterans Administration Hospital on 21 April 1975 for investigation. A heart murmur had been noted 25 years earlier. He had had episodic praecordial chest pain, unrelated to exertion, radiating to the back, left shoulder, and neck, accompanied by paraesthesiae in the left hand, with increasing

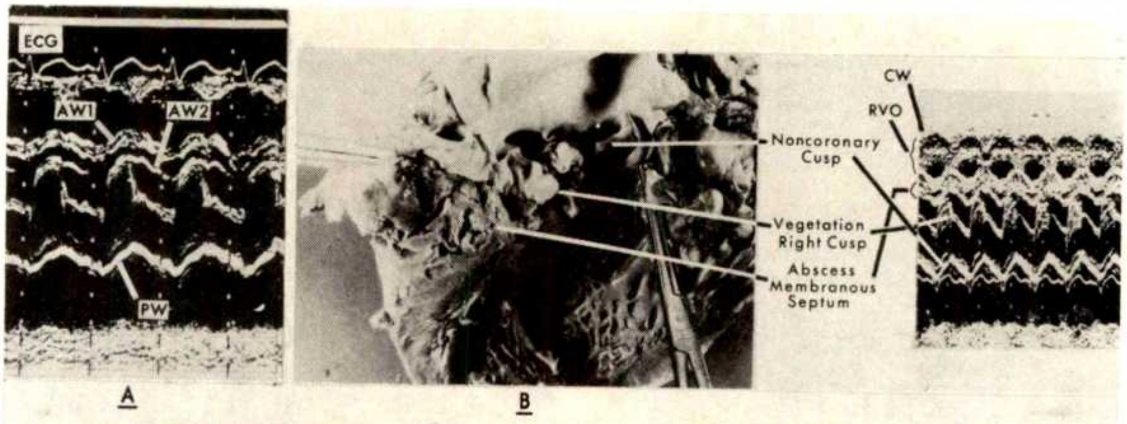

FIG. 4 *Echocardiograms in Case 2. (a) Duplication of anterior aortic wall echo; space between AW1 and AW2 is 10 mm. During systole, aortic leaflets open to posterior aortic wall (PW) and to more posterior of the two anterior aortic wall echoes. (b) Necropsy specimen correlated with high gain echocardiogram of aortic root. Mass of fluffy echoes posterior to right coronary cusp during systole is thought to come from vegetation attached to that cusp. CW = chest wall; RVO = right ventricular outflow.*

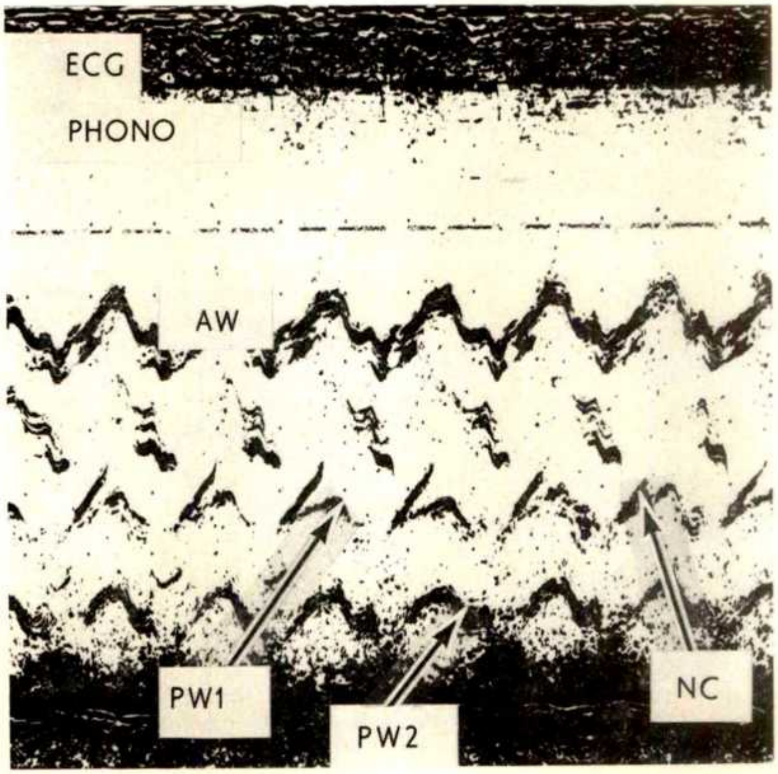

FIG. 5 *Echocardiogram of aortic root in Case 3 showing duplication of echo from posterior aortic wall (PW1 and PW2). Aortic valve opens only to more anterior of two posterior aortic wall echoes (PW1). See Fig. 1 for abbreviations.*

frequency over the past 20 years.

Blood pressure was 120/80 mmHg (16·0/10·6 kPa) in both arms and the pulse was regular at 80 beats/min. Carotid pulses were normal. An early systolic click and a grade 1/6 early diastolic blowing murmur were heard along the left sternal edge. Mild pectus excavatum was present; there was no gynaecomastia. The penis was infantile and the right testis was small and soft. There was a normal male escutcheon. VDRL was negative. The electro-

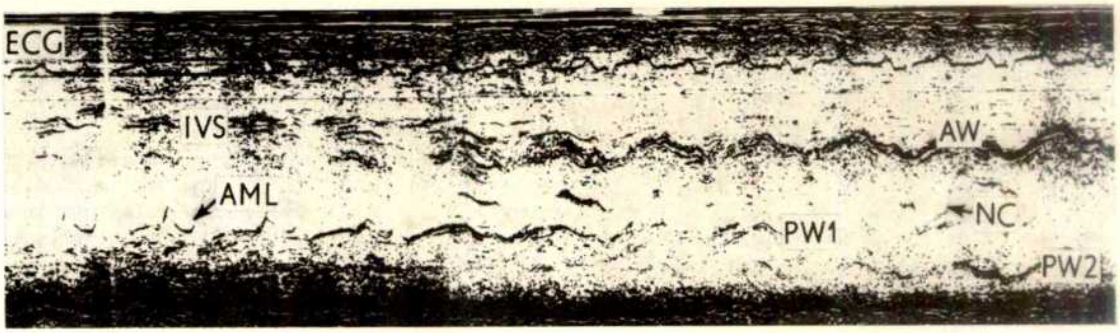

FIG. 6 *Echocardiogram in Case 3. Sweep from mitral valve (left) to aortic root (right). Continuity is shown between mitral ring and anterior (PW1) but not posterior (PW2) of two posterior aortic wall echoes. Noncoronary cusp opens only as far as PW1. AML=anterior mitral leaflet; IVS=interventricular septum.*

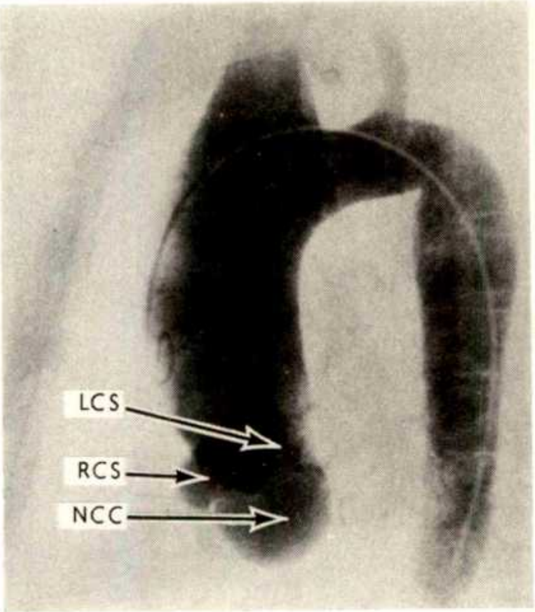

FIG. 7 *Frame from aortogram in lateral projection (subtraction technique) in Case 3 showing dilatation of aortic root and noncoronary sinus of Valsalva. No dissection is evident. LCS = left coronary sinus; RCS = right coronary sinus; NCC = noncoronary cusp.*

cardiogram was normal. Chest *x*-ray films suggested dilatation of the aortic root.

An echocardiogram showed an echo moving parallel and 15 mm posterior to that from the posterior aortic wall (Fig. 5). A sweep cephalad from the mitral ring (Fig. 6) showed continuity between the mitral ring and the more anterior of the two posterior aortic wall echoes. Because of the possibility of a chronic aortic dissection, aortography was performed; aortic root angiograms in the lateral and the right and left anterior oblique projections showed dilatation of the aortic root and noncoronary cusp of the aortic valve (Fig. 7), but an aortic dissection was not seen.

### Case 4

A 39-year-old man with severe mitral stenosis was admitted to the San Francisco Veterans Administration Hospital on 28 March 1975 for insertion of a prosthetic mitral valve. An echocardiogram performed before operation showed apparent duplication of the echo from the posterior aortic wall (Fig. 8). A sweep from the aortic root to the mitral valve (Fig. 9) showed that both apparent posterior aortic wall echoes were in fact reflections from the calcified mitral valve. The echo that probably represented the true posterior aortic wall can be seen on the sweep in Fig. 9 but is barely visible in the echocardiogram in Fig. 8.

## Discussion

The echocardiographic pattern of dissecting aneurysm involving the aortic root was first described by Millward *et al.* (1972) in a man with angiographically documented aortic dissection that had ruptured into the right atrium. The echocardiogram showed duplication of both the anterior and posterior aortic walls. The space between the inner and outer walls was thought to represent the false lumen of the dissection. Nanda *et al.* (1973) subsequently published the echocardiographic findings in 6 patients in whom aortic dissection was confirmed by angiography, surgery, or necropsy. They also showed duplication or increase in thickness of one (2 patients) or both (4 patients) aortic walls. In all 6, the aortic root was widened (42 to 53 mm outer dimension at end-systole). In 2 patients, striking variation in aortic width was seen with slight change in transducer angulation. Yuste *et al.* (1974) presented echocardiograms taken before and after repair of a dissecting aneurysm. Duplication of both aortic walls was present before and absent after operation.

Nanda *et al.* (1973) observed that widening or duplication of the aortic walls could be simulated in calcific aortic valve disease, in pericardial effusion when fluid extends into the transverse sinus, and in patients in whom a catheter has been passed into the pulmonary artery. The possibility of false-positive echocardiographic diagnosis of aortic dissection was also emphasized by Krueger *et al.* (1975), who described 2 patients with apparent thickening or duplication of the aortic wall. In 1 of these, reflection from the mitral ring was thought to be superimposed on the posterior aortic wall echo; in the second patient, the aortic wall was in fact thickened by atherosclerotic plaques.

Our findings in Case 1 (true aortic dissection) support the value of echocardiography in the diagnosis of aortic dissection. As in the case presented by Yuste *et al.* (1974), the preoperative echocardiogram showed a false lumen, which was absent in the postoperative study. It is of note that not all views of the aortic root in this patient showed duplication of the posterior aortic wall echo. The positive echocardiographic findings would easily have been missed if multiple sweeps from differing transducer positions had not been per-

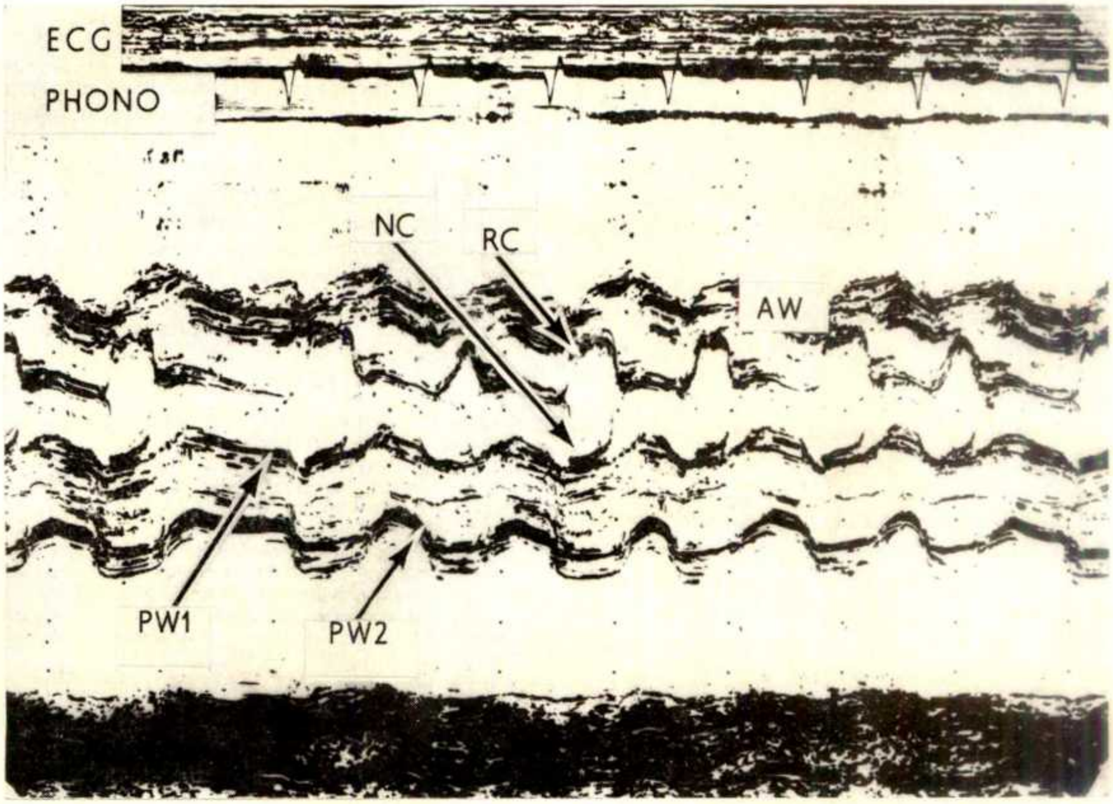

FIG. 8 *Echocardiogram in Case 4. Apparent duplication of the echo from posterior aortic wall (PW1 and PW2). See Fig. 1 for abbreviations.*

formed. The demonstration that the echo from the mitral ring diverges into two posterior wall echoes (Fig. 2c) is probably valuable in supporting a diagnosis of dissection, as suggested by Krueger *et al.* (1975). We too would urge careful scanning of the mitral ring-aortic root junction when echocardiography is used to corroborate a suspected aortic dissection.

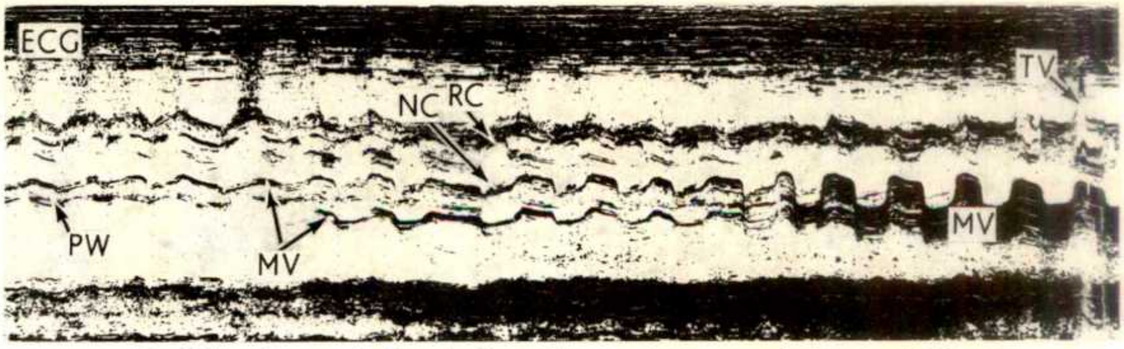

FIG. 9 *Echocardiogram in Case 4. Sweep from aortic root to mitral valve (MV). Dense echoes from calcified mitral valve are present at level of aortic valve and simulate duplication of posterior aortic wall echo. Echo that probably represents true posterior aortic wall (PW) is barely visible in middle of sweep. TV = tricuspid valve; see Fig. 1 for abbreviations.*

Case 2 (abscess in the interventricular septum) is of interest because the apparent double echo of the anterior aortic wall may have arisen from structures below the aortic valve. The septal abscess (Fig. 4) was bulging at necropsy. It is likely that a sweep from the interventricular septum to the aorta above the aortic valve would have helped to clarify the anatomy by showing convergence of the duplicate echoes into a single structure.

In the patient with aneurysmal dilatation of the ascending aorta and noncoronary sinus of Valsalva (Case 3), the reason for duplication of the posterior aortic wall echo is not clear. It is of note that in no sweep could an echo from the mitral ring be shown to divide into two separate echoes, as in Case 1. Instead, the more posterior of the two posterior aortic wall echoes invariably appeared abruptly 15 mm behind the more anteriorly placed echo; the latter was in continuity with the echo from the anterior mitral leaflet, and may have been a reflection from the mitral ring, inserting higher than normal (relative to the aortic cusps) into the fibrous tissue of the aortic root.

Case 4 (mitral stenosis) emphasized that structures adjacent to one another anatomically may appear superimposed in the echocardiogram (Feigenbaum, 1972), because of the width of the echo beam.

## Conclusions

Duplication of aortic root echoes may be helpful in corroborating the diagnosis of dissecting aneurysm involving the aortic root. However, duplicate echoes may be seen only with some transducer angulations, probably dependent on the anatomy of the false lumen. Careful attention should be paid to the junction of the mitral ring with the aortic root. Abscess in the interventricular septum and dilatation of the noncoronary sinus of Valsalva should be added to the list of conditions that may simulate aortic dissection on the echocardiogram.

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# Familial sinoatrial node dysfunction
## *Increased vagal tone a possible aetiology*

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*Clinical and electrophysiological studies of a 13-year-old boy with sinus bradycardia revealed sinus node dysfunction. Long-term follow-up data of members of his family indicated familial sinus node dysfunction. Increased vagal tone was present in all patients. It is suggested that excessive vagal discharge for a prolonged time may be the basic mechanism of sinus node dysfunction in these patients.*

Dysfunction of the sinoatrial node is being increasingly recognized in clinical practice. A variety of clinical states have been associated with the underlying pathology of the primary human pacemaker and grouped together as the sick sinus node syndrome (Ferrer, 1968). Sinoatrial node dysfunction appears not only in adults in whom there is a wide aetiological spectrum, but also in children with congenital disorders (James, 1967). This communication describes the clinical and electrophysiological features of a 13-year-old asymptomatic boy with sinoatrial node dysfunction without QT interval prolongation, congenital deafness, or any other congenital anomalies. Long-term follow-up data of members of his family indicative of familial sinoatrial node dysfunction are also presented.

## Case reports

### Case 1

A boy of 13 years 3 months was referred to the Johns Hopkins Hospital for assessment of his heart condition. The patient had been totally asymptomatic. At 3 years of age routine physical examination showed a slow irregular pulse. Since the age of 3 he was seen every year. There was no history of rheumatic fever or diphtheria. He had not received any medicines. The patient's family had a strong history of bradycardia (Fig. 1). The abnormal physical findings were limited to the cardiovascular system. The pulse rate was 40/min and irregular. Blood pressure was 135/75 mmHg (18·0/10·0 kPa). A 2-3/6 systolic ejection murmur was maximally heard at the lower left sternal border and a 1/6 mid-diastolic murmur at the apex. Chest radiograph showed a cardiothoracic ratio of 0·44 and moderately prominent pulmonary vasculature. Resting surface electrocardiogram (Fig. 2) showed sinus bradycardia at a rate of 35/min and a pattern compatible with left ventricular hypertrophy. Routine blood and urine tests were within normal limits.

Exercise increased the sinoatrial rate to 42/min; 1 mg atropine intravenously increased both the sinus and junctional rate to 50/min, with the sinus impulses capturing the ventricles resulting in a

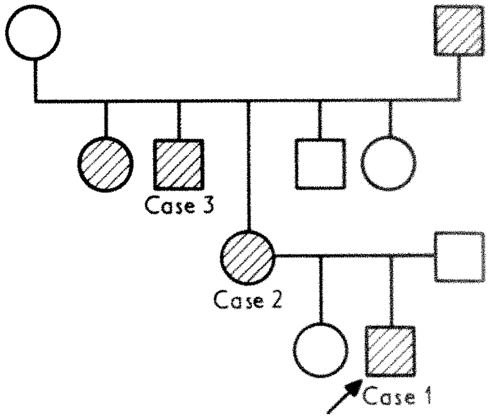

FIG. 1 *The family tree of Case 1 (identified by the arrow). The affected females and males of this family are shown as shaded circles and squares respectively.*

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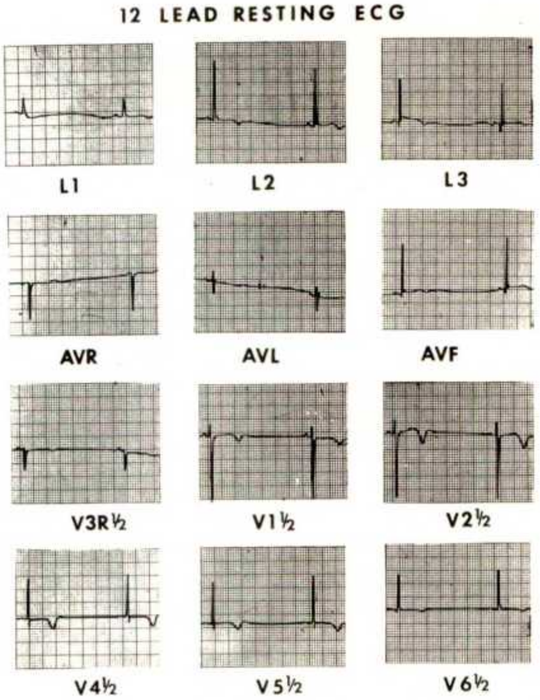

FIG. 2 *Resting 12 lead electrocardiogram of Case 1; praecordial leads were recorded on half standardization.*

bigeminal pattern with a varying degree of aberrant conduction (Fig. 3).

Cardiac catheterization was performed in the post-absorptive state; the pressure measurements were within normal limits and no gradients were found: both the cardiogreen dye curves and oximetry showed no shunt. After the intracardiac pressures were recorded a No. 6 tripolar catheter was advanced through the femoral vein across the tricuspid valve in order to record His bundle electrogram using the standard technique (Scherlag *et al.,* 1969). Another No. 6 quadripolar catheter was inserted through the right median cubital vein and advanced to the superior vena cava-right atrial junction. Two poles of this catheter were used to record a high right atrial electrogram and the other two poles were used to pace the atria. All the intracardiac electrograms, a lead II surface electrocardiogram, and time marks of 10 and 100 ms were displayed on a multichannel switched beam oscilloscope and recorded on photographic paper at a speed of 200 mm/s. The His bundle electrogram showed only a His deflection occurring before each QRS complex. Intermittently beats originating in the sinus node captured the ventricles and these beats had an AH interval of 140 ms and HV interval of 36 ms. The atria were then paced at various cycle lengths and the pacing was abruptly stopped in order to assess the automaticity of the junctional tissue and the sinus node (Mandel *et al.,* 1971; Narula, Samet, and Javier, 1972). Pacing at a cycle length of 600 ms (100/min), the first escape occurred from the junction at an interval of 1360 ms, whereas the sinus node escaped only at 3200 ms. The atria were then paced at the same cycle length after administration of 1 mg atropine intravenously. Both the junctional and sinus escape interval shortened to 778 ms and 1500 ms, respectively. After administration of atropine the frequency of both the junctional pacemaker and the sinus node increased, with the latter capturing the ventricles alternatively, resulting in a bigeminal pattern (Fig. 4). The results of the electrophysiological studies are shown in the Table.

## Case 2

The first patient's mother had been followed by a local hospital for 'left ventricular enlargement, idioventricular rhythm and possible auricular block'. She had been asymptomatic until the age of 16 years when she started having episodes of lightheadedness associated with exertion. On physical examination at the age of 19, the pulse was again noted to be irregular and slow (40/min) and a harsh nonradiating systolic murmur was present along the lower left sternal border as well as the apex; a soft mid-diastolic rumble and a wide, but physiologically split S2 was heard. Chest radiograph showed slight cardiomegaly with prominent pulmonary vasculature. Available electrocardiograms taken annually from 1953 to 1956 show junctional rhythm at a rate of 38/min and occasional sinoatrial impulses capturing the ventricles, with varying degree of aberrant conduction. The T waves were inverted in

TABLE *Results of electrophysiological studies of Case 1*

| | *Before atropine* | *After atropine (1 mg IV)* |
|---|---|---|
| Basic cycle length | 1500 ms (40/min) | 890 ms (67/min) |
| AH interval of sinus beat | 140 ms | 88 ms |
| HV interval of sinus beat | 36 ms | 28 ms |
| Atrial pacing at cycle length of 600 ms | | |
| Sinus escape time | 3200 ms | 1500 ms |
| His escape time | 1360 ms | 778 ms |
| AV node refractory period | | |
| Functional | 420 ms | |
| Effective | 250 ms | |

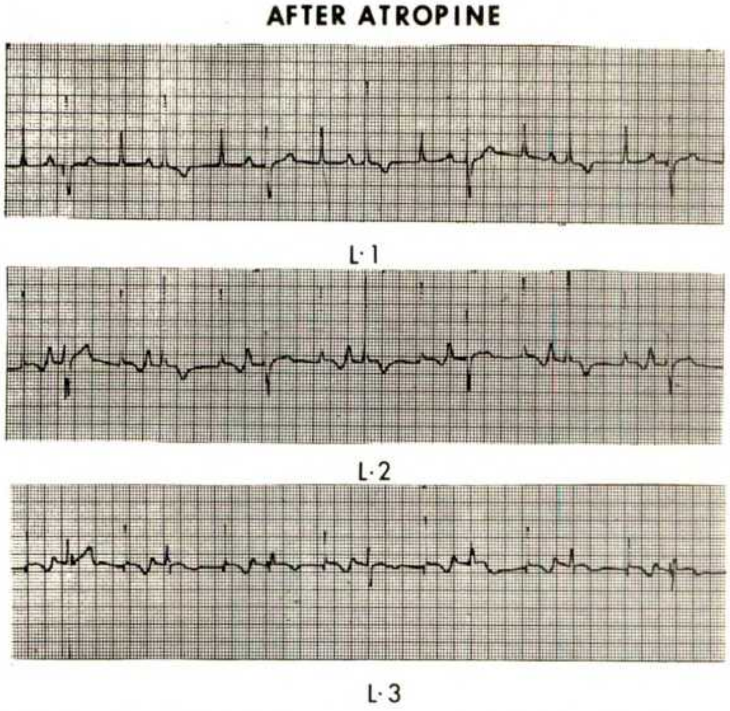

FIG. 3 *Simultaneously recorded limb leads I, II, and III of Case 1 after administration of atropine; both the junctional and the sinus rate increased, with the latter capturing the ventricles with varying degree of aberrancy.*

the praecordial leads. Atropine increased both the sinus and junctional rate to 49/min resulting in a bigeminal (sinus-junctional) pattern with higher degree of aberrant conduction than at rest. This patient continued to have exertional dizziness, and in March of 1964 she committed suicide at the age of 27.

### Case 3

The maternal uncle of Case 1 was a 28-year-old man who had been seen since his childhood by a local hospital for 'cardiac enlargement and interference dissociation'. He was known to have bradycardia from the age of 3. At the age of 19, he started having episodes of exertional dizziness, and at the age of 26 he developed syncopal episodes. Six months before being seen, he sustained multiple fractures in an accident and is now confined in a total body cast. On physical examination, the pulse was irregular and slow at 52/min, a 3/6 systolic ejection murmur was maximally heard along the upper left sternal border, a 2/6 mid-diastolic murmur was heard at the 3rd left intercostal space. The second was wide but physiologically split. Chest radiograph revealed a cardiothoracic ratio of 13/25·5 cm, without any specific chamber enlargement; the hilar areas and the central pulmonary vascular markings were prominent. Annual electrocardiograms since the age of 9 (1956) showed a junctional rhythm at a rate of 40/min, and occasional sinus impulses capturing the ventricles with varying degrees of aberrant conduction.

The mother's sister and the maternal grandfather of the first patient also had sinus bradycardia.

## Discussion

The physical findings in these patients are very similar; slow irregular pulse, forceful left ventricular impulse, harsh ejection murmur, and mid-diastolic murmur. Long cardiac cycle lengths are associated with increased atrial pressure, ventricular end-diastolic volume, and stroke volume (Tavel, 1967b). The diastolic murmur and systolic ejection murmur may result from an increase of forward blood flow, with a high velocity through the semilunar valves or the atrioventricular valves in the absence of organic stenosis (Tavel, 1967a).

Long cardiac cycle length and the associated increase in intracardiac volume can influence the cardiothoracic ratio on the chest radiograph as well as the ventricular repolarization process resulting in T wave changes of the 'volume over-load pattern'.

Bacos, Eagan, and Orgain (1960) reported the first series of familial nodal rhythm. No apparent cause was found in these patients. Spellberg (1971) reported another family with sinus node dysfunction. In both these families inheritance appears to be Mendelian dominant. This is true in our series as well.

In adults, ischaemic heart disease with involvement of the sinus node artery and degenerative changes of the sinus node have been proposed as a possible aetiology of the sick sinus node syndrome (Ferrer, 1968, 1973). Abnormalities of the sinus node artery and infarction of the sinus node have been suggested by James as a possible aetiology of congenital sinoatrial and atrioventricular block (James, 1964, 1967). However, recent coronary

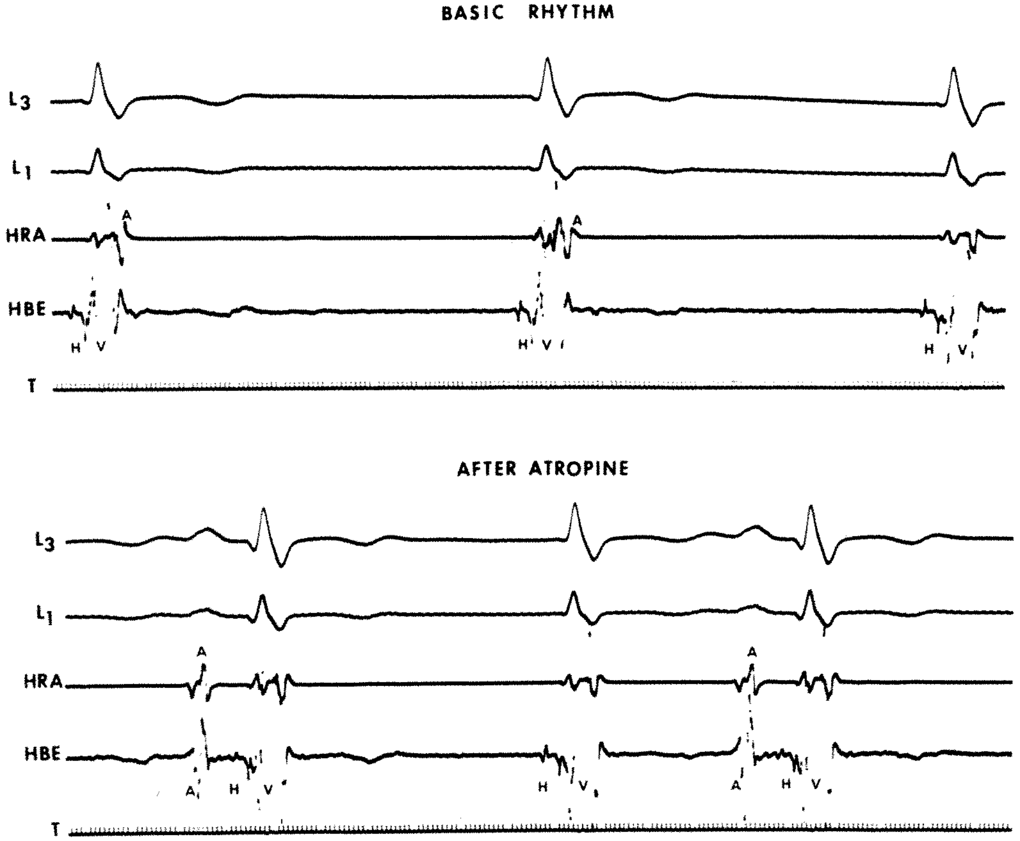

FIG. 4 *His bundle electrogram. The top panel shows the basic rhythm. The lower panel is an example of the rhythm after administration of atropine. From top to bottom (upper panel): leads III and I of the surface electrocardiogram, high right atrial electrogram (HRA), His bundle electrogram (HBE), 10 ms time lines (T). H = His deflection. V = ventricular electrogram. A = atrial electrogram. The same sequence and abbreviations are used for the lower panel. In the basic rhythm, note each QRS complex is preceded by a His deflection and has a normal HV interval. Atrial electrogram follows the QRS complex confirming that the basic rhythm originates from a junctional pacemaker. Lower panel shows the rhythm after administration of atropine; the first and the third beat originate in the sinus node as shown by an upright P wave on the surface electrocardiogram and a high-low relation of the atrial electrograms. The second beat is a junctional beat similar to that of the basic rhythm.*

artery studies by Engel *et al.* (1975) in patients with sick sinus node syndrome showed no abnormality of the sinus node artery. These authors could not exclude small vessel disease, but they concluded that coronary artery sclerosis of the sinus node artery was probably not related to the sick sinus node syndrome. If this is true for adult patients with sick sinus syndrome, ischaemic heart disease as an aetiology for familial sinus node dysfunction is extremely unlikely. Most of the patients with familial sinus node dysfunction reported developed this disorder at a very young age. In 2 of our patients sinus node dysfunction was noted at the age of 3, an unlikely age for ischaemic heart disease.

Sinus node dysfunction may occur as a result of congenital structural abnormality (James, Frogatt, and Marshall, 1967). Such abnormalities have also been seen in patients with familial atrioventricular block (James, McKone, and Hudspeth, 1975). The aetiology of these abnormalities is not clear. One wonders whether these changes could be the result of a persistent increase in vagal tone for a long period of time. Such an increase in the vagal tone for a prolonged period may result in failure of response of the P cells of the sinus node very similar to an end organ failure. In all of our patients there was evidence of increased vagal tone. All of them had pronounced sinus bradycardia as the first feature of the sinus node dysfunction and in Case 1 sinus node recovery time and the frequency of the sinus node were improved after intravenous atropine, indicative of persistent increase in vagal tone. Vagotonia was reported as a rare cause of physiological bradycardia in healthy young adults (Dighton, 1974).

Changes in the autonomic tone have been shown to occur in other familial electrocardiographic abnormalities. An example is the familial QT prolongation with or without deafness (Jervell and Lange-Nielsen, 1957; Ward, 1964). In this syndrome of prolonged QT, the QT interval can be shortened with stimulation or blocking of one or the other sympathetic chain (Moss and McDonald, 1971; Vincent *et al.*, 1974). In this condition, the recovery phase of the ventricle is prolonged as shown by the long QT interval. Experimental data from the dog and data from patients suggest that recovery phase of the ventricle is dependent on the sympathetic tone (Yanowitz, Preston, and Abildskov, 1966; Blatt, Abildskov, and Burgess, 1974). The basic mechanism of familial QT prolongation may then be an altered sympathetic tone.

It appears that familial increase in vagal or sympathetic tone may result in distinct clinical entities. An increase in vagal tone may result in familial sinus node dysfunction. The patients with familial sinus node dysfunction at a later stage may become symptomatic with bradytachyarrhythmia. Bradycardia may respond to a long-acting vagolytic agent or may require a demand pacemaker. If these patients develop tachyarrhythmias suppressive antiarrhythmic drugs in addition to pacing may be indicated.

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# Surgical treatment of pulmonary atresia with intact ventricular septum

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*Fifty-nine children with pulmonary atresia and intact ventricular septum underwent various forms of surgical treatment at the Hospital for Sick Children, Toronto, during 1950 to mid 1975. Twenty-three patients had pulmonary valvotomy, 15 direct, 2 indirect, and 6 both direct valvotomy and infundibulectomy. All died, 19 early and 4 late. Of 13 patients who received a systemic-pulmonary artery shunt, 4 combined with surgical atrial septectomy, there are only 2 long-term survivors both of whom were children who had had a Waterston anastomosis.*

*Recently we have been treating infants with small right ventricles with balloon atrial septostomy at cardiac catheterization followed by a Potts anastomosis and pulmonary valvotomy. If the Potts anastomosis appears satisfactory the persistent ductus arteriosus is ligated. This scheme was used in 23 infants, with 4 early deaths and 2 late deaths. Of 17 survivors, further shunts were required in 4 children. One child has had a formal repair, with insertion of valves in both tricuspid and pulmonary areas. We believe that this operative combination of Potts anastomosis and pulmonary valvotomy offers the infant with pulmonary atresia and a small right ventricle a relatively low initial mortality and the possibility of right ventricular enlargement and subsequent repair.*

Pulmonary atresia with intact ventricular septum is an uncommon anomaly representing 1 per cent of the total group of congenital cardiac malformations (Keith, Rowe, and Vlad, 1967). The defect is characterized by complete anatomical obstruction of blood flow from the right ventricle to the pulmonary trunk by an imperforate pulmonary valve. Systemic venous blood returning to the heart bypasses the right ventricle through an interatrial communication. Survival depends upon the persistent ductus arteriosus maintaining sufficient pulmonary blood flow; duct closure results in death. Emergency palliative operations have often been attempted but the results have until recently been poor (Gersony *et al.*, 1967; Bowman *et al.*, 1971; Cole *et al.*, 1968; Moller *et al.*, 1970).

In this paper, we report our experience with the operative treatment of pulmonary atresia with intact ventricular septum over the past 25 years.

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## Subjects and methods

From 1950 to June 1975, a total of 59 patients with pulmonary atresia and intact ventricular septum underwent surgical palliation at the Hospital for Sick Children, Toronto. All patients had preoperative cardiac catheterization and cineangiography. Diagnosis was confirmed by angiography, surgery, or necropsy. Thirty-three patients were male and 26 were female, ranging in age from 12 hours to 17 months (Table 1). Fifty-four patients (92%) had a hypoplastic, thick-walled right ventricle with a tiny lumen and 5 patients (8%) a right ventricle of moderate or large size. Of the 59 patients, 23 underwent pulmonary valvotomy, 15 direct, 2 indirect, and 6 both direct valvotomy and infundibulectomy (Table 2). Of the 59 patients, 13 received various systemic-pulmonary artery shunts, 4 of them combined with open creation of atrial septal defect. More recently 23 of the 59 patients, all with small right ventricles, have been managed by Potts anastomosis and usually ligation

TABLE 1 *Age at operation in 59 patients*

| *Age at operation* | *Number of patients* |
|---|---|
| 0–2nd week | 39 |
| 2nd–4th week | 9 |
| 1–6 months | 6 |
| >6 months | 5 |

of the persistent ductus arteriosus. Ten patients also had a pulmonary valvotomy at the same operation. All but one of the 23 had a balloon atrial septostomy (Rashkind and Miller, 1966) at the time of diagnostic catheterization.

## Results

Of the 15 patients who had direct pulmonary valvotomy with inflow occlusion, 13 died in the early postoperative period and 2 later. The longest survival time, 4 years, was related more to persistent patency of ductus arteriosus than to the opening of the pulmonary valve. In 4 patients who died, the right ventricle was of moderate or large size; 2 patients survived indirect pulmonary valvotomy (Brock procedure) for 2½ months and 8 months, respectively; 6 patients had direct valvotomy plus infundibulectomy and all died in the early postoperative period.

Nine patients received various types of systemic artery-pulmonary artery shunts. Though 7 died, 2 children who had Waterston shunts were still alive at follow-up. One of these had a pulmonary valvotomy four years after the shunt. In 4 other children a right-sided arterial shunt was combined with open creation of an atrial septal defect using inflow venous occlusion. These children were operated on before the technique of balloon atrial septostomy was described and all 4 died, either at operation or shortly after.

More recently, 23 patients had a Potts left aortopulmonary anastomosis and 10 of these also had a pulmonary valvotomy. This was usually combined with ductus ligation and preceded by a balloon atrial septostomy (Table 3). Nineteen patients survived and 4 died. Subsequently, 2 children survived cavopulmonary anastomosis (Glenn, 1958) and pulmonary valvotomy 51 months and 22 months later. Two other children required additional systemic artery-pulmonary artery shunts. One had a right Blalock-Taussig anastomosis combined with a pulmonary valvotomy six years later and the other a Waterston anastomosis and a Blalock-Hanlon atrial septectomy 20 months later. Three patients underwent pulmonary valvotomy in the late follow-up period, with 2 deaths, the only late deaths in this group. The third child survived, and in March 1974, 2 months after the pulmonary valvotomy, a repair was done in which the pulmonary and tricuspid valves were replaced with Hancock porcine valves and the right ventricular outflow tract was patched. The Potts anastomosis was closed but the atrial septal defect was left partly open because of the questionable size of the right ventricle. This patient is mildly cyanosed but doing well. There were 17 survivors in this group of 23 at the time of follow-up.

## Discussion

The size of the right ventricle has been used to classify this clinical entity into two categories (Davignon *et al.*, 1961). In one, the right ventricle is dimunitive or hypoplastic and in the second category the right ventricle is large. Variability exists between the two extremes (Gersony *et al.*, 1967; Bowman *et al.*, 1971; Murphy *et al.*, 1971). For those infants with a normal or large ventricular cavity, pulmonary valvotomy is said to be the operation of choice (Gersony *et al.*, 1967; Murphy *et al.*, 1971), though our experience suggests that

TABLE 2 *Experience with pulmonary atresia with intact ventricular septum*

| *Operative procedure* | *Number of patients* | | *Deaths* | | *Survivors* |
|---|---|---|---|---|---|
| | | | *Early* | *Late* | |
| Pulmonary valvotomy | 23 | | | | |
| Direct | | 15 | 13 | 2 | 0 |
| Indirect (Brock procedure) | | 2 | 0 | 2 | 0 |
| Direct plus infundibulectomy | | 6 | 6 | 0 | 0 |
| Systemic-pulmonary artery shunt | 13 | | | | |
| Shunt alone | | 9 | 7 | 0 | 2 |
| Shunt plus surgical septostomy | | 4 | 4 | 0 | 0 |
| Balloon atrial septostomy, Potts anastomosis, and ductus ligation (with pulmonary valvotomy 10 patients) | 23 | | 4 | 2 | 17 |
| Total | 59 | | 34 | 6 | 19 |

TABLE 3 *Clinical material and results in 23 patients who underwent balloon atrial septostomy, Potts anastomosis, and persistent ligation of ductus arteriosus*

| *Case No., sex, and age (d)* | *Date of operation* | *Remarks* | *Early results* | *Late results, follow-up* |
|---|---|---|---|---|
| 1, M, 2 | 23/12/67 | | | Mild cyanosis |
| 2, F, 19 | 5/3/68 | | | Cavopulmonary anastomosis, pulmonary valvotomy 21/6/72; moderate cyanosis |
| 3, M, 1 | 17/5/68 | | Died 2nd postop day | |
| 4, F, 5 | 13/6/68 | Normal RV | | Cavopulmonary anastomosis, pulmonary valvotomy 1/5/70; moderate cyanosis |
| 5, F, 5 | 12/11/68 | | | Right Blalock-Taussig anastomosis, pulmonary valvotomy 17/4/75; moderate cyanosis, congestive heart failure |
| 6, M, 4 | 19/1/70 | | | Pulmonary valvotomy, 11/1/73; total repair 20/3/74; mild cyanosis, congestive heart failure 20/3/74 |
| 7, F, 1 | 21/8/70 | | | Pulmonary valvotomy 26/10/71; died at operation |
| 8, M, 2 | 28/8/70 | No BAS | | Normal activity; mild cyanosis |
| 9, F, 8 | 22/1/71 | | | Marked cyanosis |
| 10, M, 7 | 12/7/71 | | Died 3rd postop day | |
| 11, F, 1 | 16/6/71 | Pulmonary valvotomy | | Mild cyanosis |
| 12, M, 2 | 28/10/71 | Pulmonary valvotomy | | Mild cyanosis; normal activity |
| 13, M, 4 | 10/1/72 | Pulmonary valvotomy | Died at operation | |
| 14, F, 6 | 2/2/72 | | | Pulmonary valvotomy 23/8/73, died at operation |
| 15, F, 0 | 27/5/72 | Pulmonary valvotomy | Died at operation | |
| 16, M, 1 | 4/4/72 | Pulmonary valvotomy | | Moderate cyanosis |
| 17, F, 2 | 4/6/73 | Pulmonary valvotomy | | Mild cyanosis |
| 18, F, 1 | 19/6/73 | Pulmonary valvotomy | | Waterston anastomosis, Blalock-Hanlon septectomy 4/3/75, moderate cyanosis |
| 19, M, 1 | 22/11/73 | | | Mild cyanosis |
| 20, F, 2 | 23/2/74 | | | Moderate cyanosis |
| 21, F, 0 | 10/12/74 | Pulmonary valvotomy | | Moderate cyanosis, congestive heart failure |
| 22, F, 44 | 14/12/75 | Pulmonary valvotomy | | Moderate cyanosis |
| 23, F, 1 | 8/5/75 | Pulmonary valvotomy | | Mild cyanosis |

a more extensive repair is often necessary. The tricuspid valve is usually abnormal, and this may be a limiting factor in early primary repair. The majority of the patients, 54 (92%) in our series, have a hypoplastic thick-walled right ventricle (Gersony *et al.*, 1967; Cole *et al.*, 1968; Shams *et al.*, 1971) with a cavity which varies from diminutive to small. Our early experience (Trusler and Fowler, 1970) and that of others (Bowman *et al.*, 1971; Murphy *et al.*, 1971; Miller *et al.*, 1973) suggests that a pulmonary valvotomy and/or infundibulectomy fail in this group because the tiny right ventricular cavity and narrow infundibular canal are incapable of accommodating adequate blood flow.

A systemic-pulmonary artery shunt, in theory, should improve children with small right ventricles. We have 2 long-term survivors who received a Waterston anastomosis. Bowman *et al.* had better long-term results when a systemic artery-pulmonary artery shunt was combined with pulmonary valvotomy.

Pulmonary atresia with intact ventricular septum and hypoplastic right ventricle is similar haemodynamically to tricuspid atresia with inadequate pulmonary blood flow. In both an adequate interatrial communication is essential to ensure right atrial exit. A balloon atrial septostomy followed by a systemic-pulmonary artery shunt has been successful in the palliative management of tricuspid atresia (Rashkind *et al.*, 1969). We have managed patients with pulmonary atresia and intact ventricular septum in this way since 1967 (Shams *et al.*, 1971; Trusler and Fowler, 1970). A balloon atrial septostomy was performed as part of the initial diagnostic cardiac catheterization on all patients but one and was followed soon after by Potts anastomosis and usually ligation of the persistent ductus arteriosus. Of 23 patients so treated there were only 4 early deaths, a mortality rate of 17 per cent.

Since 1971, in 10 children, a transarterial pulmonary valvotomy was combined with these procedures not only to decompress the right ventricle but also in the hope that the combination of pulmonary regurgitation and a shunt would stimulate right ventricular enlargement (Moller *et al.*, 1970; Bowman *et al.*, 1971; Murphy *et al.*, 1971). We prefer the Potts anastomosis for a number of reasons. The persistent ductus arteriosus can be ligated at the same operation if a suitable anastomosis is obtained, thus avoiding one factor that might cause excessive pulmonary blood flow. This may allow the operation to be performed more electively when the ductus is still large and the infant in relatively good condition. In our hands the Potts anastomosis has a higher rate of technical success and a better long-term prognosis than other shunts in early infancy. This is related to the smaller, thinner, more easily exposed descending aorta in comparison with the ascending aorta which would be used in the Waterston operation. Since we expect that some patients may benefit by subsequent cavopulmonary anastomosis (Edwards and Bargeron, 1968; Trusler, MacGregor, and Mustard, 1971) the left-sided shunt has the advantage that the right pleural space is not entered. If, on the other hand, the Fontan procedure proves to be safe and reliable over the long term for children with pulmonary atresia this will not be an advantage.

The diameter of the Potts anastomosis is an important long-term factor. It tends to enlarge with time, increasing pulmonary blood flow. To prevent excessive growth, the anastomosis is encircled or banded with a loose ring of number 2 silk. By this we hope to restrict the volume of shunt to an amount that will produce optimum palliation yet avoid heart failure and serious pulmonary vascular disease (Trusler and Kanzaki, 1973). A ring with a circumference of 25 mm allows the anastomosis to reach approximately 6 mm internal diameter. This seems adequate to perfuse the left lung ultimately should one decide to create a cavopulmonary anastomosis on the right. Further experience and longer follow-up is needed to confirm this.

Bowman *et al.* reported successful total repair in 2 patients who underwent palliation by systemic-pulmonary artery shunt and pulmonary valvotomy. The right ventricular cavity was enlarged and the pulmonary outflow tract was reconstructed with an ellipse of aortic homograft bearing a single cusp. We have one similar repair using Hancock porcine valves in both tricuspid and pulmonary positions.

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# The Wenckebach phenomenon between electric pacemaker and ventricle

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*Two cases which exhibited a Wenckebach form of exit conduction between an electrical pacemaker and the ventricular myocardium are presented. This manifests with increasing latency (stimulus to QRS intervals) and ultimate stimulus failure (block). The cycle then repeats itself. The QRS duration also increases progressively within each cycle. The phenomenon connotes an adverse prognosis. Several postulates regarding the mechanism are discussed.*

The Wenckebach phenomenon has been observed in many locations of cardiac tissue (Decherd and Ruskin, 1946; Anderson, Greenspan, and Bandura, 1970; Wennemark and Bandura, 1974; Friedberg and Schamroth, 1969; Cranefield, Klein, and Hoffman, 1971; Anderson, Greenspan, and Fisch, 1972; Rosen, 1971), and theoretically can occur in any region which conducts an activating cardiac impulse. This report concerns two instances of the Wenckebach phenomenon which occurred in the transmission of the impulse between an electrical pacemaker and the ventricular tissue. The phenomenon occurred in two seriously ill patients and presaged death in both cases. It may thus represent an important adverse prognostic sign.

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## Case reports

### Case 1

The electrocardiograms (Fig. 1 and 2) were recorded from a 61-year-old man who was admitted to hospital in shock and cardiac arrest. He had

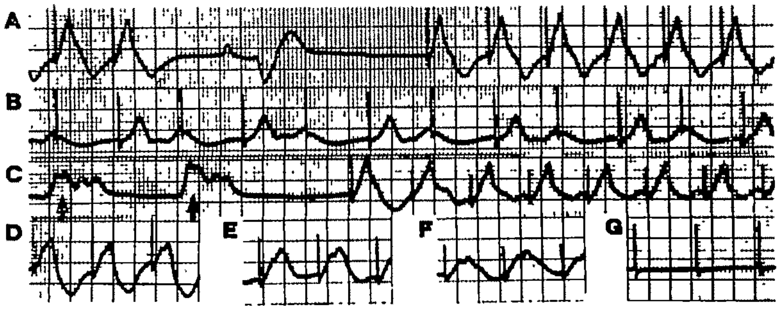

FIG. 1 *Electrocardiograms (standard lead II, recorded at a paper speed of 25 mm/s showing: Strip A. Two paced beats after which the pacemaker is turned off. This is followed by a conducted beat showing prolonged PR interval and widened QRS complex, consistent with a serum potassium of 7 mmol/l. This is followed by six further paced beats. Strip B. Electrical pacing with 2:1 pacemaker-exit block. Strip C. Cardiac arrest with cardiac massage applied during the interval between arrows. This re-establishes 1:1 conduction. Strips D-G. These illustrate decreasing amperage which results in decreasing QRS amplitude and progressive widening of the QRS complex with late peaking and eventual complete inexcitability.*

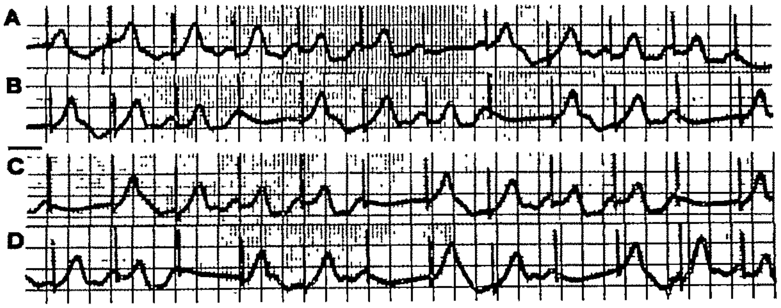

FIG. 2 *Electrocardiograms (standard lead II, strips A and B form a continuous recording; strips C and D form a continuous recording) showing: The Wenckebach form of pacemaker-exit conduction with varying conduction ratios. See text.*

chronic lung disease, and had also had an inferior wall myocardial infarction 8 years previously. The electrocardiograms were typical of hyperkalaemia, with wide and bizarre QRS complexes (analogous to the third QRS complex in strip A of Fig. 1). After resuscitation, transvenous ventricular bipolar pacing was performed (Medtronic demand pacemaker model) because of periodic complete AV block. Pacing was initially effective (strip A of Fig. 1) but soon resulted in repetitive sequences of increasing delay and second degree exit block between stimulus artefact and ventricular depolarization. Strip B of Fig. 1 illustrates sequences of 2:1 pacemaker-exit block. The first stimulus of each sequence is followed by a broad QRS complex which is in turn followed by a second deflection of the baseline. This deflection probably represents a late T wave (much less likely, though possible, a second depolarization resulting from re-entry or re-excitation). The second stimulus of the sequence occurs in the midst of this deflection and is ineffective.

Strip C of Fig. 1 illustrates the effect of cardiac massage and intracardiac catecholamine administration. These procedures re-established 1:1 conduction to the ventricle accompanied for a short time by mechanical response, only to be followed by the same electrical alterations and mechanical unresponsiveness (described below). Cardiac massage repeatedly led to the same sequence of events: return of 1:1 electrical activity and effective mechanical response; onset of electrical alterations and loss of mechanical response. Changing the output of the pacemaker conspicuously altered the QRS complex causing a decrease in amplitude and splaying out of the QRS complexes with lower electrical output (strips D and F of Fig. 1). The patient died in electromechanical dissociation in spite of all attempts, including treatment for hyperkalaemia. Strip G of Fig. 1 shows complete electrical unresponsiveness.

Tracings A and B of Fig. 2 are continuous; tracings C and D are also continuous and are from a later part of the same tracing. Strip A of Fig. 2 shows the pacemaker-ventricular Wenckebach phenomenon. The first six stimuli are followed by QRS complexes, the peaks of which (taken as a convenient reference point) are gradually and progressively more delayed. The interval between stimulus artefact and QRS complex is 40 ms and 80 ms, for the first and second stimuli, and increases to 120 ms for the sixth stimulus. The seventh stimulus falls on the T wave deflection noted previously, and fails to depolarize the ventricle. The same sequence is repeatedly observed in strips A-D, with variable conduction ratios 7:6 and 5:4 in A and C; 4:3 in B, 3:2 in D.

## Case 2

The electrocardiograms (Fig. 3 and 4) were recorded from a 61-year-old woman who was admitted to hospital with acute anterior wall myocardial infarction. Two days later, and after several episodes of ventricular tachycardia, first degree AV block appeared, with right bundle-branch block and left anterior hemiblock. This was followed shortly thereafter by complete AV block and cardiac arrest. Cardiac resuscitation and intravenous bipolar ventricular pacing were successfully carried out. After initial recovery from the cardiac arrest, the patient nevertheless remained in cardiogenic shock and congestive heart failure. Physical examination indicated a large dyskinetic ventricular area and mitral regurgitation. As early as the second hospital day, at the time of pacemaker insertion, first degree block was noted between the pacemaker and the ventricle, as reflected by a stimulus-QRS interval of 100 ms. The normal value probably does not exceed 40 ms (Brooks *et al.*, 1955; Rogel and Hasin, 1974). The tracings shown in Fig. 3 and 4 were recorded on the next—the third hospital—day. These tracings were selected from a long recording

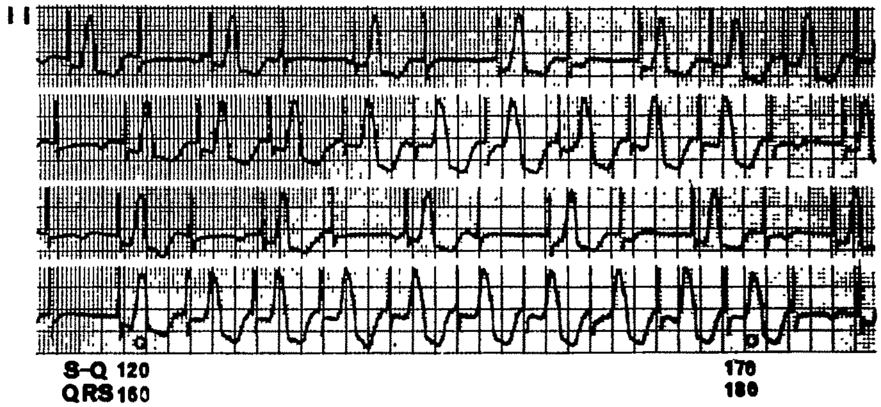

FIG. 3 *Electrocardiogram (tracings of selected segments of a continuous recording) show 2:1, 5:4, 10:9, 11:10 Wenckebach pacemaker ventricular cycles. Numbers represent measurements in ms for the two beats marked by circles. Note that the last RR interval of each series is shorter than the first. See text.*

of standard lead II. The first eight stimuli in the top strip of Fig. 3 were conducted with a 2:1 pacemaker-ventricular exit block. The last four stimuli of this strip all depolarized the ventricles with a Wenckebach form of exit block. The SQ intervals increased progressively from 120 ms to 160 ms, to be followed by a blocked stimulus (not shown). The blocked stimulus at the beginning of the second strip was followed by a Wenckebach sequence with a 10:9 conduction ratio. The SQ intervals increased progressively from 120 ms to 180 ms to be followed by a blocked stimulus. The third strip once again reflected 2:1 pacemaker-ventricular exit block. The last strip reflected a 11:10 Wenckebach conduction cycle. The SQ intervals increased progressively from 120 to 170 ms to be followed by a blocked stimulus. The duration of the QRS complexes also increased slightly from 160 to 180 ms (complexes labelled with a circle in the bottom strip of Fig. 3). The first RR interval of each sequence (strips 2 and 4) is the longest, with a subsequent shortening. Fig. 4 shows the dependence of the SQ delay and QRS duration on rate and current strength. Strips A reflect the effect of

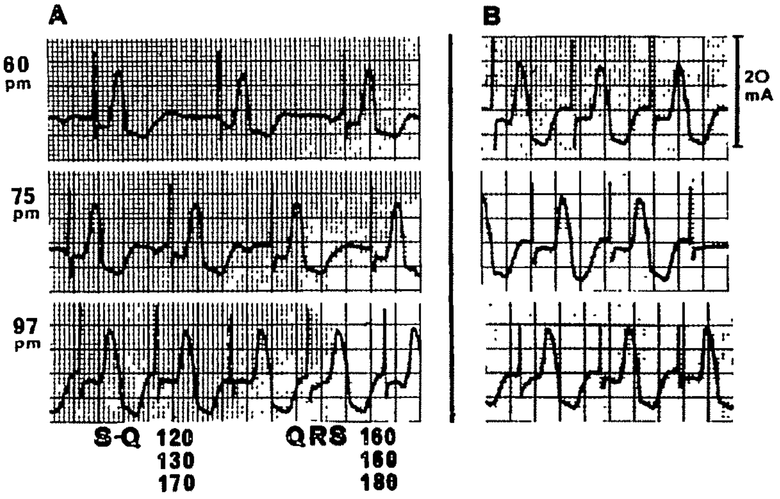

FIG. 4 *Electrocardiograms illustrating the effect of (A) changing rate, and (B) varying amperage on latency and QRS width. See text. Measurements in tracings are in ms and apply to the first and last complexes of each strip.*

rate: as the rate is increased, both the S-Q intervals and QRS duration increase. Strips B reflect the effect of variable current strength: as amperage was decreased (from top to bottom strips), the SQ interval increased from 160 ms (top strip) to 200 ms (middle strip). The last stimulus in the middle strip is ineffective. A maximum amperage of 20 mA (top strip in B of Fig. 4) resulted in a 1:1 response with first degree exit block. Several attempts were made to modify the electrical behaviour by repositioning the pacemaker electrode tip, but the same phenomenon was observed repeatedly. The patient died in intractable ventricular failure on the 19th day in hospital, two weeks after the onset of the Wenckebach phenomenon. Necropsy showed extensive myocardial necrosis and fibrosis of the anterior and lateral walls, the apex, septum and papillary muscles of the left ventricle, and severe diffuse coronary artery disease.

### Patient studies

Attempts at altering latency (SQ interval) and reproducing the Wenckebach phenomenon were carried out in 5 paced patients with chronic AV block and presumably normal myocardium. In all these patients, excitatory threshold was less than 0·5 mA, with bipolar stimulating electrodes similar to those used in the two previously described patients. The current strength was decreased in a stepwise fashion till excitation threshold was reached, while the electrocardiogram was recorded at 50 mm/s speed to obtain accurate measurement of the SQ interval. In none of the patients was there a significant increase in the SQ interval with decreasing current strength. At threshold current strength, occasional stimuli successfully depolarized the ventricles. In none of these was the SQ interval significantly different from those obtained at greater current strength. In no instance was a Wenckebach phenomenon observed. In one patient the configuration of the QRS complex was altered but the SQ interval remained constant.

## Discussion

### Significance of the SQ duration (latency)

The sequences of gradually increasing stimulus-ventricular delay (increasing SQ interval) followed by a blocked stimulus reflect a Wenckebach form of pacemaker exit block. The classical Wenckebach progressive shortening of the RR intervals (an acceleration of the tissue activation distal to the block) is also evident in these cases.

The SQ interval is here referred to as *latency*. This comprises (a) the time required for depolarization of the tissue immediately in contact with the stimulating electrodes (true latency) which is dependent on the current strength of the stimulus, (b) the time required for the local electrical response to break out of the vicinity of the stimulating electrodes, and (c) the time required to depolarize sufficient myocardial mass to cause the onset of the QRS complex. Normal values for the SQ interval are difficult to find in published reports. Our observations lead us to believe that it is usually not more than 40 ms. Similar values were seen experimentally by Brooks and associates (1955), and Rogel and Hasin (1974). Increased SQ duration indicates an increase in one or more of the aforementioned time factors, and occurs as a result of severe myocardial depression. This was the result predominantly of severe hyperkalaemia in the first case, and to diffuse myocardial disease in the second.

Dependence of latency on current amplitude is well known (Brooks *et al.*, 1955; Hoffman and Cranefield, 1960), and is clearly documented in both these cases. Threshold stimuli excite surrounding myocardium more slowly than suprathreshold stimuli. Very strong suprathreshold stimuli can also directly stimulate a larger area around the electrodes than threshold stimuli. It is thus the *distance* which the propagated impulse has to travel which is decreased with suprathreshold stimuli.

Several theories have been postulated to explain the mechanisms underlying classic Wenckebach periodicity which has not, as yet, been completely elucidated (Wennemark and Bandura, 1974; Cranefield *et al.*, 1971; Anderson *et al.*, 1972; Rosenblueth, 1958; Watanabe and Dreifus, 1967; Damato *et al.*, 1972). The mechanism of a pacemaker-ventricular Wenckebach phenomenon is also uncertain but could possibly be explained on the basis of one or more of the following factors.

(1) The phenomenon could be the result of a gradually increasing block around the electrode site with each successive beat, a phenomenon similar to that seen in the classic form of AV nodal Wenckebach periodicity.

(2) The phenomenon could be the result of a gradual decrease in the effectiveness of each succeeding stimulus to break out of the immediate electrode area into surrounding myocardium. Stimuli are initially suprathreshold, but become successively less effective, and, therefore, threshold and eventually subthreshold. As a result, a progressively smaller area of myocardium is directly excited with each successive stimulus. More and more myocardial

mass is thus dependent on secondary *propagated* excitation and less and less on direct *stimulation*. This difference may be negligible in healthy myocardial tissue. In depressed myocardium, however, in which propagated excitation may proceed in a very non-homogeneous manner, this could result in variable delays with pronounced differences in the SQ interval.

(3) The phenomenon could possibly result from time-dependent (rather than voltage-dependent) refractoriness, extending well beyond the end of the T wave so that succeeding impulses occur progressively earlier in the refractory period. The Wenckebach phenomenon in Case 1 represents a relatively simple instance in which there is gradual encroachment of the refractory period of the gradually delayed ventricular depolarization upon the time of arrival of the succeeding stimulus as postulated by Rosenblueth (1958).

## Significance of varying QRS duration

The duration of the QRS complex also increases within each Wenckebach cycle, as well as with decreased amperage and increased rate of stimulation, as seen in Fig. 1, 3, and 4. This is similar to bundle-branch Wenckebach periodicity. This increase could again result from (a) a time increase in intraventricular conduction time, or (b) a gradual decrease in the size of initial directly depolarized ventricular mass by the electrical stimulus, with greater reliance on non-homogeneous propagated excitation through depressed fibres.

It is thus evident that Wenckebach periodicity of both SQ intervals and QRS duration is the end product of very intricate, interrelated disturbances in refractoriness, responsiveness, latency, conduction characteristics, amplitude of electrotonic spread, and threshold potential in depressed fibres. Depression of the myocardium is undoubtedly a *sine qua non* for an interventricular Wenckebach phenomenon. Our attempts at recording it in patients with chronic complete AV block but normal or relatively normal myocardium have been unsuccessful. It has to our knowledge never been observed with normal or relatively normal myocardium. On the other hand, 'first degree' pacemaker to myocardium exit block has been observed by us in a patient with extremely severe congestive heart failure and the sick sinus syndrome, and in another two patients with severe hyperkalaemia. Both cases presented here indicate severe myocardial dysfunction, and in one, the appearance of the Wenckebach phenomenon anticipated death by 15 days, suggesting that it may be an additional, useful prognostic sign in the management of acute cardiac emergencies.

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# Quantitative radionuclide angiocardiography
## *Determination of left ventricular ejection fraction in children*

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*A method is described for measuring left ventricular ejection fraction which uses high frequency computer recording of gamma scintillation camera data and peripheral venous injection of technetium-99m as sodium pertechnetate. Data from mechanical model experiments are used to show feasibility of this method. A phantom experiment is described which was used to develop a technique for accurate delineation of the ventricular outline in the presence of background. The left ventricular ejection fraction was measured in 12 patients by radionuclide angiocardiography and biplane cineangiography. Comparison of these two methods gave a correlation coefficient of 0·91. In addition, left ventricular ejection fraction was measured in 34 patients (aged 7 weeks to 18 years) without evidence of cardiac disease using the radionuclide method alone. Average ejection fractions of 0·66 and 0·70 were found for children over 2 years of age and children 2 years of age or younger, respectively. In addition, an interobserver comparison study was performed with the data from 10 patients, and only small differences were noted (SD 0·025).*

Clinical assessment of left ventricular ejection fraction as a measure of ventricular performance is of value in the management of patients with heart disease. In the past, this measurement has been made by contrast angiography at cardiac catheterization. More recently, a number of techniques have been described which use radionuclides to measure left ventricular ejection fraction. Strauss *et al.* (1971) described the use of the electrocardiogram to control time intervals for the collection of end-diastolic and end-systolic images in the gamma camera during equilibrium of an intravascular radioindicator. The volumes and ejection fraction were then calculated from the area and length of the ventricular images (area-length method). Van Dyke *et al.* (1972) described the use of a television monitor recording from oscilloscope images of the first passage of a radionuclide through the left heart. They used a single 'region-of-interest' over the ventricular image to determine the relative end diastolic and end-systolic counts. They then used an extraventricular region-of-interest to determine the level of background radiation and subtracted this from the end-diastolic and end-systolic counts before calculating ejection fraction (background-subtraction method). Reports by other workers (Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975) have described modifications of these two methods, using improvements in equipment and details of technique. The most recent report, that of Schelbert *et al.* (1975), shows excellent results in comparison with contrast angiography using a background-subtraction technique similar to that of Van Dyke *et al.* (1972).

However, there remain problems with these two basic techniques. Both methods, especially the former, are sensitive to choice of area, and neither has a generally-accepted method of making that choice. The latter method has the disadvantage that there is no justifiable *a priori* way of selecting the background region-of-interest; hence this is chosen empirically.

The purpose of this report is to present a new technique for the measurement of left ventricular ejection fraction. The method involves choosing separate areas for end-diastole and end-systole in a clearly-defined way. The counts in each region

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during the respective cardiac phases are then used to calculate ejection fraction. This method differs from the area-length method in that the counts, rather than the areas, are used in the calculation; this gives the area a third dimension (i.e. count density). It differs from the background-subtraction method in that no area for determination of background is used; instead, different areas are used for end-systole and end-diastole rather than a single area for both. This avoids the difficult problem of empirical choice of background area. The specific technique for defining areas was developed using a series of phantom experiments, and the method was compared to contrast angiography in 12 patients. In addition, the normal range was established in 30 children.

## Materials and methods

All radionuclide studies were performed using intravenous technetium-99m as sodium pertechnetate and recording with a gamma scintillation camera[1] interfaced with a digital computer system.[2] Recording was done on an event-by-event basis (list mode); the studies could be framed at a variety of frame rates for display on the computer oscilloscope in a 64 × 64 matrix.

To ensure that this equipment was adequate for the recording of rapidly changing images, a test was performed using a mechanical model of the ventricle.[3] The model was set at a variety of heart rates and ejection fractions, and computer recordings were made of a bolus of 10 mCi of Tc-99m flowing through it without recirculation at each setting. The recordings were framed at 10 frames/second, and ejection fractions were measured using the counts within the 'ventricle' at end-diastole and end-systole from the formula: ejection fraction = (end-diastolic counts − end-systolic counts)/(end-diastolic counts). Actual and measured ejection fractions (the latter averaged over 10 beats) were in close agreement.

The next task was to develop a consistent method of outlining the ventricle in the presence of background. First, five consecutive patient studies were examined to determine the amount of background. Intrathoracic count rates outside the left heart and aorta were found to average about 18 to 33 per cent of the maximum intraventricular count rate during end-diastole. The extracardiac activity remained constant from end-diastole to end-systole, though of course the intraventricular counts decreased. From this it was decided to perform a static phantom experiment with containers of various sizes, using constant background levels of 15, 25, and 35 per cent of the maximum counts in the largest container; this spanned the entire range of patient study background levels. Containers with 100 ml, 50 ml, 40 ml, 30 ml, and 20 ml of water mixed with technetium-99m were imaged in the presence of these background levels. They were also imaged without background to determine the actual count rates. From these latter measurements, the actual 'ejection fractions' were found from the counts in the smaller containers and those in the largest container; this number could then be compared with the 'ejection fractions' measured in the presence of background. The images of the containers with background were displayed and, with the computer, isocount contours at percentages of the maximum count rate were superimposed. Outlines of the containers were drawn using these contours, and the counts inside them were totalled. These totals were used to calculate 'ejection fractions', as in the non-background case for each of five different isocount contour levels (75%, 65%, 55%, 45%, and 35%).

Twelve patients aged 2 to 40 years (mean 20) were examined by both cardiac catheterization and radionuclide angiocardiography. Four of the radionuclide angiocardiography studies were performed in the catheterization laboratory; the rest were done on the morning after catheterization. Catheterizations were performed for the usual indications, and informed consent was obtained for radionuclide angiocardiography.

The angiograms were done with either biplane cineangiography at 60 frames/second or biplane cut film[1] at 6 frames/second, with simultaneous recording of the electrocardiogram. Most volumes were calculated by the length-area method of Dodge *et al.* (1960), with two corrections: (1) a mathematical correction for magnification assuming a point source and linear spread, and (2) Graham's correction for ventricular wall irregularities (Graham *et al.*, 1971). In 3 cases, the Simpson's rule method of Chapman *et al.* (1966) was used. The left ventricular ejection fraction (EF) was calculated from the volume by the formula: EF = (end diastolic volume − end-systolic volume)/(end-diastolic volume).

The radionuclide angiocardiograms were performed with a peripheral venous injection. The dose of Tc-99m as sodium pertechnetate was 200 μCi/kg; specific activity was 20–60 mCi/ml. Recordings were made event by event (list mode) with the camera and computer system described above.

[1] Nuclear Chicago Pho/Gamma HP, Chicago, Ill., or Nuclear Data Radi-camera.

[2] Gamma-11 (DP 11/20) Digital Equipment Corporation, Maynard, Mass.

[3] Thermo-Electron Corporation, Waltham, Mass.

[1] Elema-Schonander, Sweden.

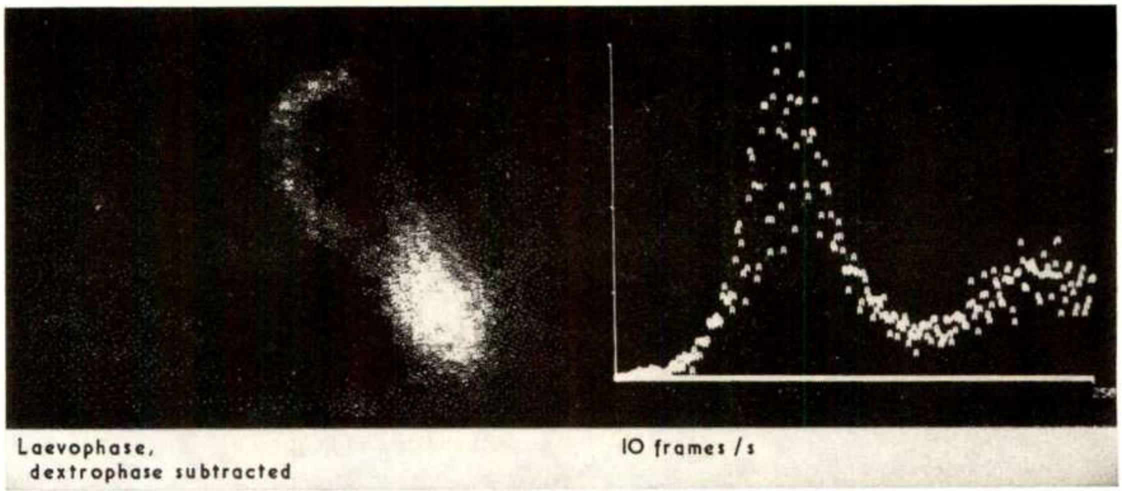

FIG. 1 *Left: Two second scintigraph (64 × 64) of the left ventricular and aortic activity. The scintigraphic frames corresponding to the superior vena cava, right atrium, right ventricle, and pulmonary artery were subtracted in the computer. Right: Time-activity curve at 10 frames per second obtained from a region-of-interest placed over the left ventricle.*

Imaging was done in the anterior position. The data were framed at 10 frames/second in a 64 × 64 matrix unless the heart rate was greater than 120, for which framing was done at 15 frames/second. The next step was to choose end-diastolic and end-systolic frames. This was done using the computer display by placing a region-of-interest for time reference over the left ventricle as seen on a 2-second summed image of the laevophase of radionuclide passage with the dextrophase subtracted. The number of counts in this region in each frame of the study was displayed graphically (Fig. 1), and equal numbers of end-diastolic and end-systolic frames were chosen from the peaks and troughs of this graph. By summing the frame matrices corresponding to these peaks and troughs, composite pictures were obtained of end-diastole and end-systole (Fig. 2). The planes of the aortic and mitral

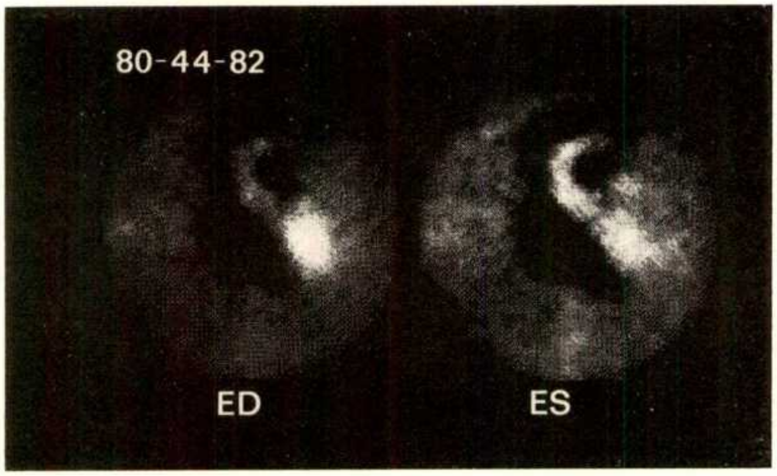

FIG. 2 *End-diastolic (left) and end-systolic (right) frames composed of 10 heart beats. Note the 'filling' of the ascending aorta with activity on the end-systolic frame. The frames corresponding to the superior vena cava, right atrium, right ventricle, and pulmonary artery were subtracted.*

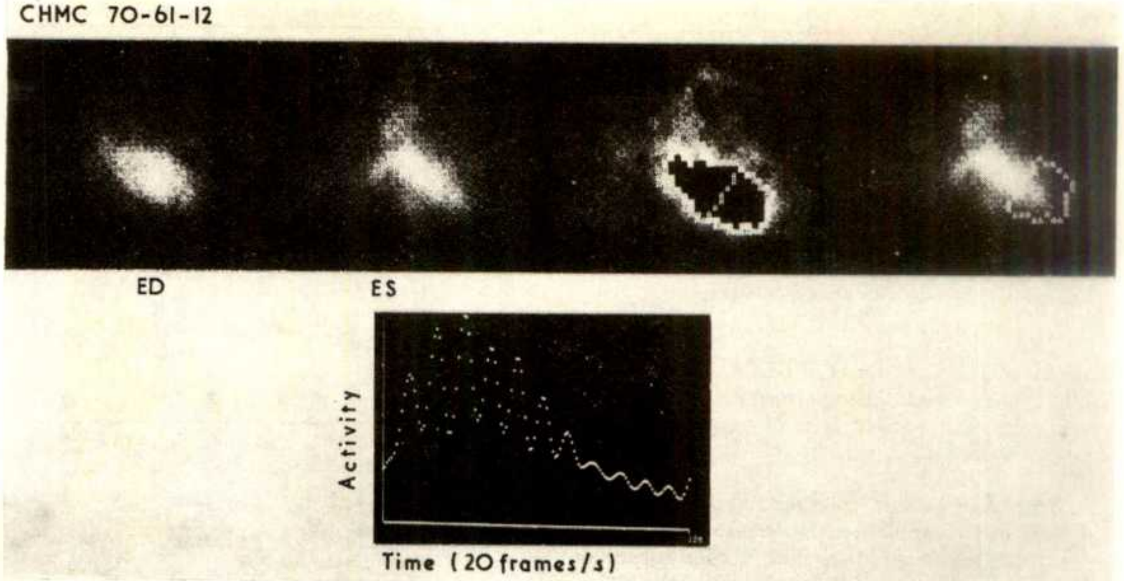

FIG. 3 *Top row: End-diastolic (ED) frame, end-systolic (ES) frame, end-diastolic frame with an isocount contour of 55 per cent of the intraventricular maximum with end-diastolic region of interest superimposed and end-systolic frame showing the left ventricular outline within the end-diastolic region-of-interest. Bottom row: Time-activity curve at 20 frames per second after filtering with Fast Fourier Transform.*

valves were chosen directly from the end-diastolic composite. Then, the isocount contour at 55 per cent of the intraventricular maximum was displayed on each of the composite pictures, and, with the valve planes superimposed, the remainders of the end-diastolic and end-systolic areas were chosen (Fig. 3). In cases where the isocount contour was irregular, a smooth outline was chosen such that its area was identical to that inside the contour.

Since previous workers (Strauss *et al.*, 1971; Van Dyke *et al.*, 1972; Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975) have used various methods of combining cardiac cycles to yield the ejection fraction, the counts were obtained using these regions-of-interest in two ways: (1) placing the regions-of-interest over the summed diastolic and systolic frames as described and determining the counts within them ('static' method); (2) using the areas similarly to calculate an average beat-by-beat ejection fraction, using only the 3 beats including and after the bolus peak ('dynamic' method). In each case the ejection fractions were calculated from the formula: EF = (end-diastolic counts − end-systolic counts)/(end-diastolic counts). The final ejection fraction was taken as the average of these two numbers.

An additional 34 children (aged 7 weeks to 18 years, mean 9 years) without evidence of cardiac disease were studied. All were scheduled for non-cardiac radionuclide studies using Tc-99m as pertechnetate (brain and abdominal studies) or as diphosphonate (bone studies). In this way a group of 'normal' values was obtained without additional radiation exposure.

No attempt has been made to correct the dead-time losses. Though such a correction was considered, analysis of actual patient data made it clear that any such correction would be very small. Though high total count rates which cause dead-time losses were found in these studies, the rates do not change in a systematic way from diastole to systole. Thus, any such multiplicative correction factors would be nearly identical for systole and diastole, and would cancel when the ejection fraction was calculated.

A frequency analysis technique using the Fast Fourier Transform (FFT) (Brigham, 1974) for the time-activity curves for the regions as described was also developed. By eliminating the higher frequencies from these curves, a smooth clear curve could be obtained. This technique was tested in 15 patients.

The effect of choice of isocount contour was

TABLE 1 *Phantom experiment results*

| *Threshold used* | *Mean absolute error* | *Root mean squared error* |
|---|---|---|
| 75% | 0·0725 | 0·0951 |
| 65% | 0·0319 | 0·0422 |
| 55% | 0·0237 | 0·0266 |
| 45% | 0·0256 | 0·0335 |
| 35% | 0·0314 | 0·0385 |

*Note:* Errors are comparisons of measured vs. actual 'ejection fraction' averaged over all containers and all background levels (total: 12 measurements for each average).

assessed in 12 patients. Calculations of ejection fraction were made using isocount contours of 45 per cent and 65 per cent of maximum intraventricular counts, as well as the standard 55 per cent.

A 'two independent observer' correlation study was done in 10 consecutive patients to test the consistency of the technique. The second observer (L.O.) was not a medically-trained person.

In addition, ejection fraction was calculated by the method described by Schelbert *et al.* (1975) in 15 patients for comparison with this method. The only differences between the Schelbert method as described and that applied here was that imaging was done in the anterior position and injections were in a peripheral vein rather than in the superior vena cava. Six of these patients had intracardiac left-to-right shunts and 9 did not.

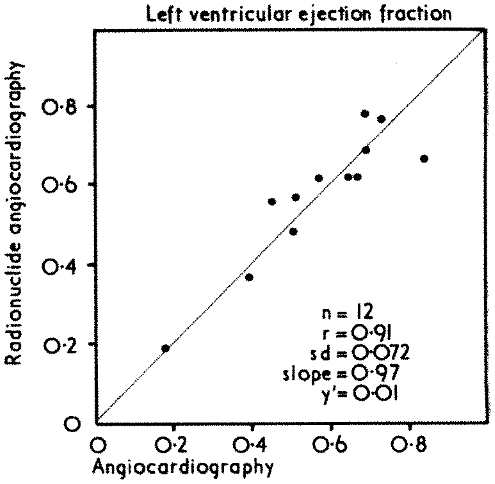

FIG. 4 *Comparison of left ventricular ejection fraction in 12 patients estimated by radionuclide angiocardiography and during angiography at catheterization.*

## Results

The results of the phantom experiment are shown in Table 1, which shows the average error of the measured vs. actual 'ejection fraction' for the five different isocount contour levels. The most accurate choice was 55 per cent; however, 45 per cent was not significantly worse. The former level was

TABLE 2 *Left ventricular ejection fraction determined by left ventricular angiography and radionuclide angiocardiography*

| *Case No.* | *Age (y)* | *Diagnosis* | *Ejection fraction Radionuclide angiocardiography* | | | *Biplane angiocardiography* |
|---|---|---|---|---|---|---|
| | | | *Static* | *Dynamic* | *Mean* | |
| 1 | 18 | MR; s/p coarctation repair; aortic valvotomy | 0·79 | 0·78 | 0·78 | 0·69 |
| 2 | 18 | s/p DORV repair | 0·59 | 0·65 | 0·62 | 0·57 |
| 3 | 10 | cardiomyopathy | 0·18 | 0·19 | 0·19 | 0·18 |
| 4 | 3 | s/p TGA repair | 0·67 | 0·67 | 0·67 | 0·84 |
| 5† | 38 | PFO; persistent LSVC; AS; AR | 0·57 | 0·66 | 0·62 | 0·67 |
| 6† | 23 | AS; AR | 0·69 | 0·68 | 0·69 | 0·69 |
| 7† | 40 | CAD | 0·48 | 0·48 | 0·48 | 0·50 |
| 8† | 21 | s/p FT repair | 0·54 | 0·60 | 0·57 | 0·51 |
| 9† | 39 | s/p ventricular aneurysm repair | 0·38 | 0·35 | 0·37 | 0·39 |
| 10 | 23 | AS; AR | 0·56 | 0·56 | 0·56 | 0·45 |
| 11 | 6 | VSD; AR | 0·61 | 0·63 | 0·62 | 0·65 |
| 12 | 6 | s/p TGA repair | 0·77 | 0·78 | 0·77 | 0·73* |

MR = mitral regurgitation; TGA = transposition of great arteries; PFO = patent foramen ovale; LSVC = left superior vena cava; CAD = coronary artery disease; AS = aortic stenosis; AR = aortic regurgitation; FT = Fallot's tetralogy; DORV = double outlet right ventricle; VSD = ventricular septal defect.

*Only single plane available for ejection fraction calculation. †Radionuclide angiocardiography performed in catheterization laboratory. s/p = postoperative state.

TABLE 3 *Left ventricular ejection fraction estimated by radionuclide angiocardiography in 25 patients without cardiovascular disease*

| *Patient* | *Age (y)* | *Heart rate* | *Ejection fraction* | | |
|---|---|---|---|---|---|
| | | | *Static* | *Dynamic* | *Average* |
| 1 | 14 | 60 | 0·65 | 0·64 | 0·64 |
| 2 | 6 | 107 | 0·61 | 0·61 | 0·61 |
| 3 | 6 | 100 | 0·62 | 0·60 | 0·61 |
| 4 | 7 wk | 89 | 0·72 | 0·70 | 0·71 |
| 5 | 13 | 91 | 0·81 | 0·78 | 0·79 |
| 6 | 15 | 86 | 0·75 | 0·75 | 0·75 |
| 7 | 13 | 107 | 0·73 | 0·75 | 0·74 |
| 8 | 11 | 80 | 0·74 | 0·74 | 0·74 |
| 9 | 9 | 100 | 0·70 | 0·71 | 0·70 |
| 10 | 4 | 106 | 0·69 | 0·68 | 0·69 |
| 11 | 13 | 105 | 0·57 | 0·58 | 0·57 |
| 12 | 7 mth | 185 | 0·73 | 0·79 | 0·76 |
| 13 | 10 | 111 | 0·70 | 0·71 | 0·70 |
| 14 | 12 | 92 | 0·62 | 0·62 | 0·62 |
| 15 | 5 | 92 | 0·54 | 0·53 | 0·53 |
| 16 | 2 | 89 | 0·66 | 0·67 | 0·66 |
| 17 | 17 | 67 | 0·62 | 0·64 | 0·63 |
| 18 | 8 | 124 | 0·67 | 0·69 | 0·68 |
| 19 | 7 | 71 | 0·60 | 0·60 | 0·60 |
| 20 | 8 | 93 | 0·58 | 0·56 | 0·57 |
| 21 | 6 | 107 | 0·69 | 0·70 | 0·70 |
| 22 | 15 | 95 | 0·70 | 0·74 | 0·72 |
| 23 | 8 | 103 | 0·67 | 0·72 | 0·69 |
| 24 | 2 | 153 | 0·59 | 0·65 | 0·62 |
| 25 | 8 | 86 | 0·74 | 0·72 | 0·73 |
| 26 | 16 | 77 | 0·58 | 0·64 | 0·61 |
| 27 | 11 | 83 | 0·67 | 0·70 | 0·69 |
| 28 | 5 | 97 | 0·61 | 0·62 | 0·62 |
| 29 | 11 | 71 | 0·64 | 0·63 | 0·64 |
| 30 | 6 | 150 | 0·71 | 0·73 | 0·72 |
| 31 | 12 | 82 | 0·59 | 0·60 | 0·60 |
| 32 | 14 | 97 | 0·70 | 0·74 | 0·72 |
| 33 | 18 | 100 | 0·67 | 0·64 | 0·66 |
| 34 | 9 | 92 | 0·56 | 0·58 | 0·57 |

chosen by operator preference to be used in all patient studies.

The comparison study data are shown in Table 2, along with pertinent patient information. Ejection fraction by angiography is plotted against ejection fraction by radionuclide angiocardiography in Fig. 4. The correlation coefficient was 0·91, and the standard deviation 0·072. Note that there is one patient in whom a large difference between angiography and radionuclide angiocardiography was found; this patient had partial obstruction of the superior vena cava, and thus had a slow bolus, with unusually high background levels which partially obscured the regions.

The ejection fractions measured in the 34 children without known heart disease are shown in Table 3. The average was found to be 0·66 ± 0·065 (SD) in the 30 children over 2 years. This is statistically significantly higher ($P < 0{\cdot}05$) than the average of 0·63 ± 0·05 (SD) reported by Graham *et al.* (1971) for children aged 2 to 18. Our average for the children of 2 years and under was 0·70 ± 0·05 (SD), but as there were only 4 children in this group, no meaningful comparison can be made with the published value (0·68 ± 0·05) (Graham *et al.*, 1971).

The Fast Fourier Transform smoothing technique made only slight differences in the calculation of the ejection fraction in the 15 patients in whom it was tested; on average, it changed the measured ejection fraction by only −0·009, with a range from −0·030 to +0·020. Because of the time-consuming nature of this method and its small contribution, the technique was not adopted.

The testing of different isocount contours for the selection of regions-of-interest resulted in modest changes in the calculated ejection fraction. As one would expect, using the 45 per cent instead of the 55 per cent contour yielded lower ejection fractions, since both the end-diastolic and end-systolic area increased in size. The average decrease was 0·022 for the 12 cases; the ejection fraction actually increased in 3 cases. Similarly, when the 65 per cent contour is used, one would expect an increase in ejection fraction from the 55 per cent contour. The average increase was 0·032 for the 12 cases; decreases occurred in only 3 cases.

The results of the two-observer correlation study are shown in Table 4. The average absolute difference was only 0·019, and the standard deviation of the regression line only 0·025.

TABLE 4 *Interobserver correlation in estimation of left ventricular ejection fraction by radionuclide angiocardiography*

| *D.K.* | *L.O.* |
|---|---|
| 0·66 | 0·70 |
| 0·62 | 0·63 |
| 0·66 | 0·67 |
| 0·59 | 0·59 |
| 0·58 | 0·56 |
| 0·70 | 0·74 |
| 0·70 | 0·73 |
| 0·67 | 0·67 |
| 0·54 | 0·56 |
| 0·70 | 0·67 |

Comparison of measured ejection fractions from identical data in 10 patients by two independent observers.

Results obtained with the background subtraction method of Schelbert *et al.* (1975) compared quite closely with those using our method in the 9 patients without left-to-right shunts. The average absolute difference was only 0·027, and the square root of the mean squared error was 0·038 over a range of ejection fractions of about 0·5 to 0·8. Overall, Schelbert's method gave ejection fractions 0·022 higher than those from our method for non-shunt patients. However, in the patients with left-to-right shunts, the ejection fractions from the background subtraction technique averaged 0·077 above those from this technique. The range of ejection fractions for this latter group was about 0·6 to 0·8. This difference between the shunt and non-shunt patient groups, though small, was statistically significant ($P < 0·01$), despite the small sample sizes.

## Discussion

The static phantom experiment shows that it is possible to use isocount contours to measure relative counts in the presence of background with good accuracy. The 45 and 55 per cent isocount contours give the best results; the 55 per cent contour has the advantage that the regions tend to be less irregular, thus making the outlining process easier.

The close correlation between ejection fraction from radionuclide angiocardiography and from conventional angiography compares well with that found in other studies (Strauss *et al.*, 1971; Van Dyke *et al.*, 1972; Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975). Since this technique was to be applied to children aged 2 to 18, it would have been preferable to make the comparison in patients of that age. Unfortunately, in our centre, few catheterized children have low ejection fractions; for this reason, 6 adults with a wide range of ejection fractions were catheterized in addition to the 6 children in order to validate the technique.

'Normals' in our study had significantly higher average ejection fraction than the normal value obtained from contrast angiography. There is, of course, no way of telling whether this is the result of a systematic error in one technique or the other, or whether it reflects some effect of contrast medium (Karliner, Bouchard, and Gault, 1972).

One of the most important features of this technique is the interobserver correlation. The average difference of only 1·9 per cent is considerably smaller than that of 5·4 per cent reported by Schelbert *et al.* (1975). The primary reason for this is probably the precise standardization of this technique.

The high correlation between this technique and that of Schelbert *et al.* (1975) in non-shunt patients is also important. Without many more studies with correlations with catheterization, it would not be possible to determine which technique is better in non-shunt patients.

The difference between this technique and that of Schelbert *et al.* (1975) in the shunt patients is also significant. Since the background area as described by Schelbert includes lung and right heart, anything which increases the activity in these structures relative to the left heart would tend to increase the measured ejection fraction. Since intracardiac shunts have this effect, an increase in measured ejection fraction by the background subtraction technique might be expected. However, the difference could also be the result of decrease in measured ejection fraction by our technique, resulting from the presence of higher background activity.

The technique of smoothing curves by removing high frequencies using the Fast Fourier Transform is potentially useful. It could be used as part of an automatic procedure to eliminate spurious peaks or troughs resulting from statistical fluctuation.

## Conclusion

A new method of measuring left ventricular ejection fraction by radionuclide angiocardiography has been developed. This method overcomes the problem of empirical choice of background area. Details of the technique were refined using phantom experiments, and the method was validated by comparison with contrast angiography in 12 patients. Regression analysis on these data yielded the correlation coefficient $r = 0{\cdot}91$. A normal range of $0{\cdot}66 \pm 0{\cdot}065$ (SD) for children aged 2 to 18 years has been established. Measurements by two independent observers showed excellent correlation, with average differences of only 1·9 per cent. A good correlation between this method and another radionuclide method (Schelbert *et al.*, 1975) has been shown in patients without intracardiac shunting. However, a significant difference was found between the two techniques in patients with intracardiac shunts; this is not yet explained.

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# Prevention of balloon damage during initiation of intra-aortic balloon counterpulsation

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*Damage to an intra-aortic balloon occurred on two occasions in 93 insertion procedures. The complication was recognized before gas embolization occurred, and neither patient suffered ill effects. On both occasions the balloon was holed when pinched by artery forceps applied to the 'dacron' graft.*

Rupture of an intra-aortic balloon is the most obvious potential complication of arterial counterpulsation. The rarity of this event is a tribute to surgical care and to the design and construction of currently available intra-aortic counterpulsation systems. However, despite care in surgical technique, balloon rupture can occur during insertion of the catheter and could conceivably be lethal if not recognized immediately and if safety mechanisms are overridden during initiation of counterpulsation.

Balloon rupture occurred twice during 93 catheter insertion procedures by eight operators over four years. The balloon was damaged in the same way on both occasions when artery forceps were applied to the 'dacron' graft to assist in pulling this over the balloon onto the catheter shaft. Our experience is reported so that others may avoid the same error.

## Case reports

### Case 1

A 47-year-old man was admitted in cardiogenic shock and the decision was made to initiate counterpulsation. Difficulty was experienced in pulling the 8 mm I.D. 'dacron' graft over the 40 ml balloon selected. Artery forceps were applied to the edge of the graft as it lay on the balloon and were used to complete the procedure. The catheter was inserted to the correct position using the technique described by Kantrowitz *et al.* (1968) and connected to the console. Before proceeding further, blood was detected in the catheter tubing. The catheter was removed and another inserted without incident and counterpulsation was started with good effect. The first catheter was found to have a small round defect, approximately 1 mm in diameter, in its balloon some 6 cm from the distal end. Observers suspected but could not be certain that artery forceps had nipped the balloon and torn the hole.

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### Case 2

A 55-year-old man was admitted in acute pulmonary oedema complicating myocardial infarction. Medical therapy was judged to have failed and the patient was prepared for counterpulsation. A 40 ml balloon catheter was selected, and again difficulty was experienced in threading the balloon through the 8 mm 'dacron' graft. Again, artery forceps were applied to the graft as it lay on the balloon and the procedure was completed. The catheter was inserted and connected to the console. The catheter was purged with helium gas and counterpulsation was started with the safety switch in the manual mode. After some 15 to 20 seconds, blood was seen in the catheter tubing.

Counterpulsation was discontinued, the catheter was removed, and another introduced. The patient's condition did not change in any way. Counterpulsation was then restarted, with good effect. The original balloon catheter appeared intact but on testing under water, a small leak was detected in a position similar to that in Case 1. Microscopical examination showed the tear with accompanying marks that could only be attributed to the forceps.

## Discussion

Damage to an intra-aortic balloon catheter by a sharp instrument has been described on one occasion (Scheidt *et al.,* 1973). We have been meticulous with respect to sharp instruments and during the insertion procedures have not permitted these to be used near the balloon once it has been removed from its sheath. Damage from a blunt instrument is unexpected. On both occasions described here the arterial graft was grasped by the forceps as it lay on the redundant folds of the balloon and the balloon was inadvertently holed. This manoeuvre, which we consider to be dangerous, is shown in Fig. 1. Fig. 2 shows the recommended procedure for applying the arterial graft. The graft (which should be as wide and as short as practicable) is grasped at one end by at least three forceps before being applied to the balloon, then gently eased over the balloon. We urge that forceps never be applied to the graft once the graft has been placed on the balloon.

The complications described here were poten-

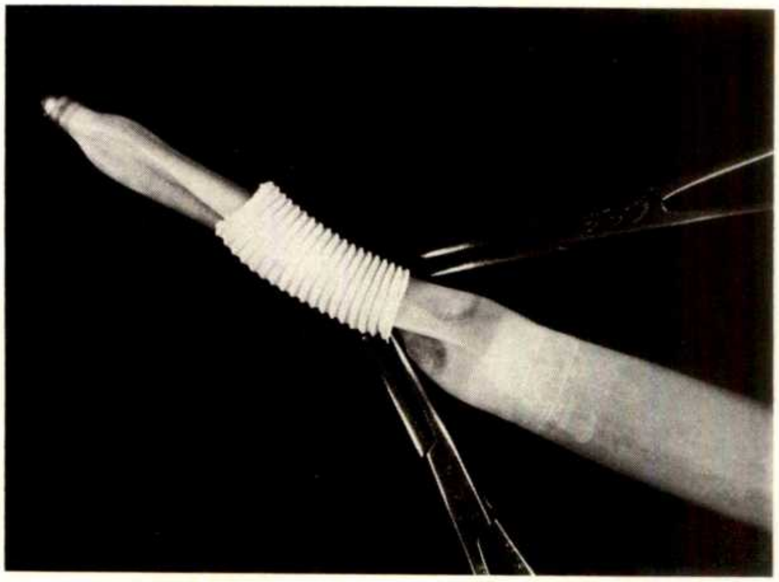

FIG. 1 *The dangerous technique of graft placement.*

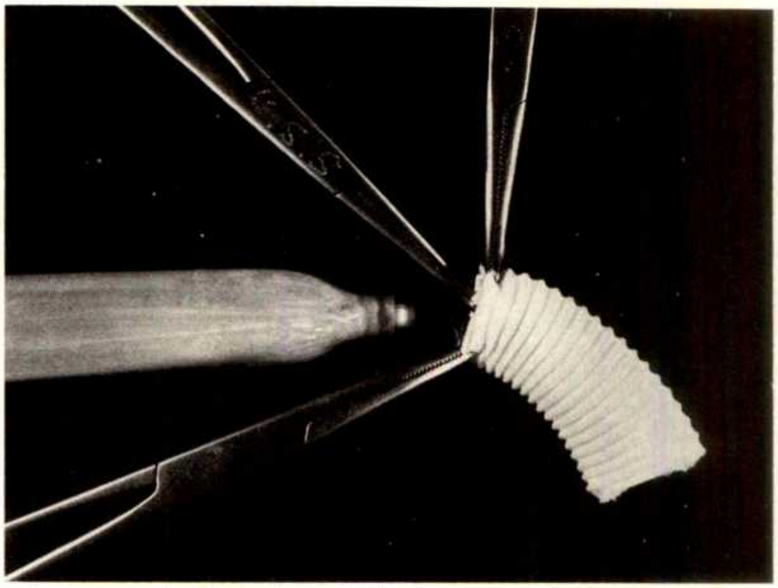

FIG. 2 *The recommended technique of graft placement.*

tially the most serious we faced in four years' experience with intra-aortic counterpulsation. We report these complications trusting that they will be kept in proper perspective—complications that need not have occurred and in 93 desperately ill patients, the only immediately life-threatening side effects of an important new life-saving technique.

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# Haemolysis after mitral valve replacement with the Björk-Shiley and the Lillehei-Kaster disc valve prosthesis

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*The present study reports on the incidence and degree of intravascular haemolysis in 33 patients with Björk-Shiley tilting disc prosthesis and in 34 patients with Lillehei-Kaster pivoting disc valve prosthesis in the mitral position examined 12 to 24 months after the operation. Serum haptoglobin, serum lactate dehydrogenase, serum bilirubin, and haemoglobin estimations were performed. Significant haemolysis was detected in 85 per cent of the patients. Haptoglobin was absent or reduced in 72 per cent, while raised values for serum lactate dehydrogenase were found in 43 per cent. The increase in lactate dehydrogenase was moderate and showed no correlation with blood flow through the prosthesis or with the gradient across the prosthesis. Most patients had normal haemoglobin and normal serum bilirubin values.*

*Although intravascular haemolysis was of little clinical significance, the increase in lactate dehydrogenase was significantly higher in patients with the Lillehei-Kaster prosthesis than in patients with the Björk Shiley prosthesis, indicating a slightly shorter red cell lifespan in the former group. The possible reasons for the difference between the two groups are discussed.*

Intravascular haemolysis after heart valve replacement has been reviewed by several investigators since the initial report by Rose *et al.* (1954). Though the problems of haemolysis are better known in patients with an aortic valve prosthesis the occurrence of mild haemolysis is not unusual after mitral valve replacement with a Starr-Edwards prosthesis (Walsh, Starr, and Ritzman, 1969), a Smeloff-Cutter prosthesis (Milam *et al.*, 1969), or a Kay-Shiley prosthesis (Vogel *et al.*, 1969). The purpose of the present study was to assess the incidence and severity of chronic haemolysis in patients with one or other of the two new disc valve prostheses, the Björk-Shiley tilting disc valve and the Lillehei-Kaster pivoting disc valve.

## Subjects and methods

The present report is based on studies of 67 unselected patients with isolated mitral valve replacement. There were 27 men and 40 women, varying in age between 33 and 65 years, with a mean age of 56·8 years. In 33 patients, the prosthesis inserted was a Björk-Shiley tilting disc valve[1] (Björk, 1972), while in 34 patients a Lillehei-Kaster pivoting disc valve was used (Lillehei *et al.*, 1970). The valve sizes used are presented in the Table.

TABLE *Sizes of prosthetic valves used*

*Björk-Shiley prosthesis*

| *Valve size* | *Orifice area* (cm²) | *No. of patients* |
|---|---|---|
| 25 | 3·2 | 3 |
| 27 | 3·8 | 2 |
| 29–31 | 4·6 | 28 |

*Lillehei-Kaster prosthesis*

| *Valve size* | *Orifice area* (cm²) | *No. of patients* |
|---|---|---|
| 18 | 2·5 | 4 |
| 20 | 3·1 | 8 |
| 22 | 3·8 | 11 |
| 25–28 | 4·9 | 11 |

The re-examination took place 12 to 24 months after the operation. During the observation period all patients were on maintenance treatment with

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[1] Pyrolite carbon disc.

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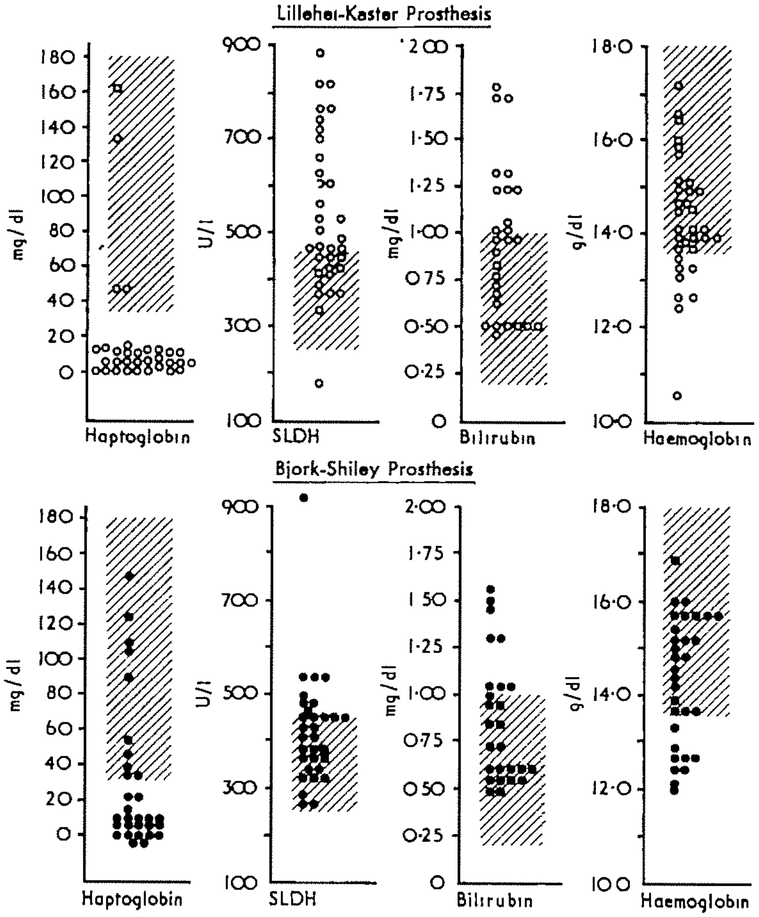

FIG. 1 *Serum haptoglobin, serum lactate dehydrogenase (SLDH), serum bilirubin, and haemoglobin concentration in patients with Lillehei-Kaster (above) or Björk-Shiley (below) prosthetic valve. The shaded area marks normal range.*

digitoxin, diuretics, and anticoagulant agents. None of these patients received iron supplements.

To assess possible haemolysis, the following laboratory tests were performed: haemoglobin concentration by cyanmethaemoglobin method (normal range 13·5 to 18·0 g/dl), serum bilirubin by Jaffe's reaction (normal range 0·2 to 1·0 mg/dl), haptoglobin by saturation with haemoglobin and measuring of the peroxidase activity (normal range 30 to 180 mg/dl), and lactate dehydrogenase (SLDH) activity in serum using Kabi's reagents (normal range 150 to 450 u/l).

In addition to investigation for evidence of haemolysis in all patients, postoperative haemodynamic data were available in most patients: these included resting cardiac output (Fick's principle) and mean diastolic pressure gradient across the mitral valve determined by planimetric integration of simultaneously recorded pulmonary artery wedge pressure and left ventricular pressure after correction for delay. Left ventricular cineangiography showed a normally functioning prosthetic valve. There was no evidence for gastrointestinal bleeding, infection, or drug allergy in any patient.

Arithmetical means, standard deviations, and coefficients of correlations were calculated as described by Snedecor (1956). Regression lines were drawn according to equations found by the method of least squares. Statistical significance of differences between means was made using Student's t-test. P values higher than 0·05 were not considered to be significant.

## Results

Of the 67 patients studied, 57 (85%) showed one or several unequivocal signs of intravascular haemolysis. Fig. 1 shows the individual data for haptoglobin, lactate dehydrogenase, and bilirubin in serum, and haemoglobin, in patients with a Björk-Shiley or Lillehei-Kaster prosthesis.

Haptoglobin was absent or greatly reduced in 48 (72%) of the patients studied. The mean value for haptoglobin was 31·0 mg/dl in patients with a Björk-Shiley prosthesis and 15·8 mg/dl in patients with a Lillehei-Kaster prosthesis. The number of patients without haptoglobin was approximately the same in both groups. SLDH values were raised in 29 (43%) of the patients studied. The mean value for SLDH was 425·5 ± 124·8 U/l in patients with a Björk-Shiley prosthesis and 533·5 ± 162·6 U/l in patients with a Lillehei-Kaster prosthesis, showing significant higher values in the latter group ($t=2{\cdot}973$, $P<0{\cdot}01$). Seventeen patients (25%) had a raised serum bilirubin level. Of these 17 patients, 16 had additional signs of haemolysis, while one patient (bilirubin 1·8 mg/dl) showed no other indication of haemolysis. The mean value was 0·87 ± 0·32 mg/dl in patients with Björk-Shiley prosthesis and 0·92 ± 0·39 mg/dl in patients with Lillehei-Kaster prosthesis. The intergroup difference was not significant ($t=0{\cdot}490$, $P>0{\cdot}05$). Seventeen (25%) of the patients examined had abnormal low values for haemoglobin. Of these 17 patients, 13 had additional signs of haemolysis, while 4 showed no other indications of haemolysis. The mean value for patients with a Björk-Shiley prosthesis was 14·32 ± 1·34g/dl, and for patients with a Lillehei-Kaster prosthesis 14·27 ± 1·31 g/dl. The intergroup difference was not statistically significant ($t=0{\cdot}138$, $P>0{\cdot}05$).

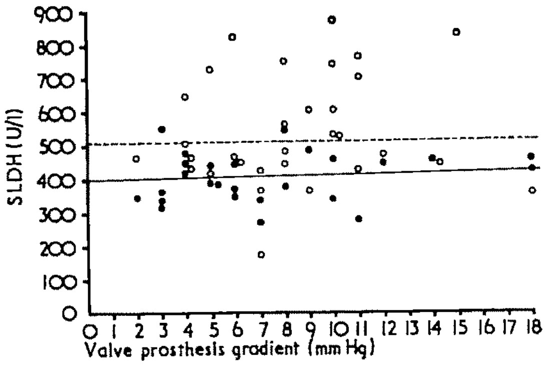

FIG. 3 *Plot diagram with regression lines showing the relation between SLDH and gradient across prosthetic valve. Open circles-Lillehei-Kaster prosthesis: regression line* $y=2{\cdot}4\times+513{\cdot}0$, $r=0{\cdot}051$, $P>0{\cdot}05$ *(interrupted line). Closed circles-Björk-Shiley prosthesis: regression line* $y=2{\cdot}0\times+386{\cdot}9$, $r=0{\cdot}124$, $P>0{\cdot}05$ *(solid line).*

Fig. 2 shows that there is no correlation between flow through the prosthesis (cardiac output) and the severity of haemolysis as assessed by the SLDH levels. As seen in Fig. 3, SLDH values in both groups of patients varied independently of the diastolic gradient across the valve.

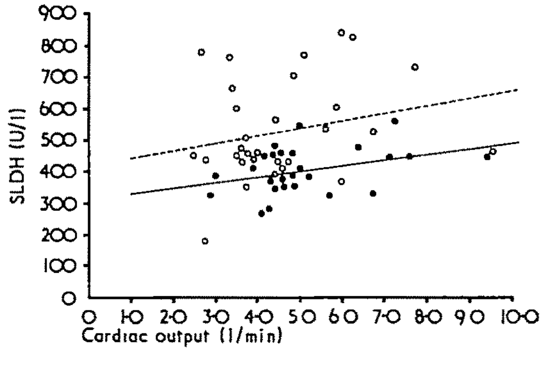

FIG. 2 *Plot diagram with regression lines showing the relation between SLDH and cardiac output in patients with prosthetic valve. Open circles-Lillehei-Kaster prosthesis: regression line* $y=36{\cdot}8\times+366{\cdot}1$, $r=0{\cdot}368$, $P>0{\cdot}05$ *(interrupted line). Closed circles-Björk-Shiley prosthesis: regression line* $y=18{\cdot}2\times+308{\cdot}1$, $r=0{\cdot}383$, $P>0{\cdot}05$ *(solid line).*

## Discussion

Chronic haemolytic anaemia is an unwanted effect of prosthetic replacement of cardiac valves. In this type of haemolysis the SLDH is increased because of enzyme liberation from damaged erythrocytes, and the degree of rise in SLDH levels correlates with the degree of shortening of the $^{51}$Cr red cell survival time (Walsh *et al.*, 1969; Myhre, Rasmussen, and Andersen, 1970). Free plasma haemoglobin liberated from ruptured erythrocytes binds to haptoglobin or is excreted by the kidney when the plasma haemoglobin level exceeds the binding capacity of haptoglobin. Serum haptoglobin is usually absent or much reduced in the presence of moderate continuous haemolysis (Eyster, Mayer, and McKenzie, 1968; Myhre, Dale, and Rasmussen, 1971). Hyperbilirubinaemia is a more uncommon finding, since only slight to moderate extravascular haemolysis is seen in patients with a prosthetic valve (Wallace *et al.*, 1970a; Wallace, Kenepp, and Blakemore, 1970b). Anaemia is present in only a small percentage of cases.

In the present study, clinically manifest haemolysis in the form of haemolytic anaemia was not seen in any patient. Mild haemolysis, however, was present in the majority, as shown by slightly increased SLDH and decreased haptoglobin concentrations

Interestingly, we were able to show differences between the two types of prosthetic valves used. Patients with a Lillehei-Kaster prosthesis were apparently more predisposed to haemolysis than patients with a Björk-Shiley prosthesis. Perhaps the most widely accepted theory is that destruction of erythrocytes after replacement with a valve prosthesis is the result of an increase in shearing stress from turbulence and from increased diastolic or systolic gradient (Nevaril *et al.*, 1968). The two types of disc valve used in the present study are both characterized by a central flow pattern with little turbulence. Furthermore, the mitral valve is situated in a relatively low pressure system and is less likely to produce the shearing stress required to damage red cells. In our study, increased concentrations of serum lactate dehydrogenase showed no significant correlation with either the peak diastolic gradient across the valve or the flow through the valve.

Most probably, the difference in severity and incidence of haemolysis between patients with a Björk-Shiley prosthesis and those with a Lillehei-Kaster prosthesis is related to differences in valve design. While the Lillehei-Kaster pivoting disc valve closes completely during ventricular systole, there is slight regurgitation at the periphery of the Björk-Shiley disc valve after closure; this has been calculated to be about 5 per cent of the forward stroke volume (Björk, 1975). It is possible that the mechanical trauma to the red blood cell is less in this non-overlapping valve compared with an overlapping valve prosthesis, and that crushing of the erythrocytes between the disc and the valve seat may explain the more severe haemolysis seen in patients with the Lillehei-Kaster valve.

There is no significant difference between the results of the present study and those of a previous investigation of haemolysis after insertion of a Björk-Shiley or Lillehei-Kaster prosthesis in the aortic position (Nitter-Hauge *et al.*, 1974). Apparently, the position of the prosthesis is of only minor importance in this connexion. Similarly, no difference has been observed between mitral and aortic Starr-Edwards valves (Crexells *et al.*, 1972), though these valves in general were more traumatic to red cells than the disc valves used by us.

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# Lack of effect of bed rest and cigarette smoking on development of deep venous thrombosis after myocardial infarction

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*In a prospective study of patients admitted to a coronary care unit, the incidence of isotopically diagnosed deep venous thrombosis was found to be related to the severity of illness rather than to the duration of bed rest. In addition, no negative correlation was found between cigarette smoking and deep venous thrombosis.*

Bed rest is considered to be an important predisposing cause of venous thrombosis (Gibbs, 1957). In patients who have had a myocardial infarction, figures for isotopically-diagnosed venous thrombosis have varied widely, with reported frequencies as low as 12 per cent but as high as 38 per cent (Murray *et al.*, 1970; Wray, Maurer, and Shillingford, 1973; Warlow *et al.*, 1973; Simmons, Sheppard, and Cox, 1973; Habersberger, Pitt, and Anderson, 1973; Marks and Emerson, 1974). The recommended period of bed rest after a myocardial infarction has also varied widely (Groden, Allison, and Shaw, 1967; Hayes, Morris, and Hampton, 1974), and it remains unclear whether the risk of venous thrombosis is associated with the severity of the underlying illness or with prolonged immobility and bed rest to which the more seriously ill patient may be subjected.

During a comparative study of patients with uncomplicated myocardial infarction mobilized after 2 or 9 days (Hayes *et al.*, 1974), we used the $^{125}$I-labelled fibrinogen uptake test to determine the frequency of venous thrombois. In addition, we studied the frequency of venous thrombosis in patients whose myocardial infarctions were complicated by heart failure, arrhythmia, or persistent chest pain, and the frequency in patients admitted to a coronary care unit because of chest pain but who were eventually found not to have had a myocardial infarct. We have also considered the suggestion that cigarette smokers with myocardial infarction develop venous thrombosis less frequently than non-smokers (Marks and Emerson, 1974; Handley and Teather, 1974).

## Patients and methods

For one year, all patients admitted to the coronary care unit (CCU) at Nottingham General Hospital were considered for entry into a mobilization study. All such patients had a history suggestive of myocardial infarction but the diagnosis was only accepted if characteristic electrocardiographic abnormalities occurred or there was a rise in serum enzymes [creatinine kinase (CK), aspartate aminotransferase (AST), lactic dehydrogenase (LD), or hydroxybutyric dehydrogenase (HBD)]. At 48 hours after admission to hospital, patients with a definite myocardial infarction were divided into 'complicated' and 'uncomplicated' groups. Patients with proven myocardial infarction were placed in the 'complicated' group if they had persistent chest pain, heart failure (judged clinically by the presence of breathlessness, a raised jugular venous pressure, triple rhythm, and basal crepitations or by radiological evidence of pulmonary oedema), or a significant arrhythmia. Any arrhythmia requiring treatment at 48 hours, or a sinus tachycardia of greater than 110 beats/minute was considered significant. Patients without complications were randomly allocated to a 2- or 9-day mobilization programme according to a ward rota (Hayes *et al.*, 1974). Accordingly four groups of patients were derived as follows:

*Group 1:* Complicated myocardial infarction.

*Group 2:* Uncomplicated myocardial infarction, mobilized after 2 days.

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*Group 3:* Uncomplicated myocardial infarction, mobilized after 9 days.

*Group 4:* Chest pain not caused by myocardial infarction.

In groups 1 and 4 no specific mobilization programme was followed, but a record was kept of the first day on which the patients were allowed to walk around the ward.

The study consisted of 266 patients, all of whom had given informed consent, who were assessed for the incidence of isotopically diagnosed venous thrombosis.

$^{125}$I-labelled fibrinogen was obtained from the Radiochemical Centre, Amersham. Each patient received an intravenous injection of 100 μCi of the labelled fibrinogen within 36 hours of admission to hospital, with the exception of 5 patients in whom the injection was delayed until 72 hours. Isotope scanning using a Pitman 235 localization monitor was done daily (excluding weekends) for 10 days, unless death supervened. Legs were scanned at 5 cm intervals from the level of the popliteal fossa to the ankle and a diagnosis of venous thrombosis was made if a difference in uptake of 20 per cent or more was shown between adjacent sites on the calf or a corresponding position on the opposite limb which persisted for at least 24 hours. The day on which a scan became positive was related to the date of admission to hospital and not to the date of isotope injection.

## Results

A total of 266 patients with a suspected myocardial infarction were admitted to the CCU during the study period and were scanned. Table 1 compares the four groups of patients at their formation 48 hours after admission to hospital. Patients in group 1 (complicated myocardial infarction) had a significantly greater mean AST level (251 ±25 IU) than the patients in groups 2 and 3 (151 ±99 and 146 ± 109 IU respectively). There was also a significantly greater number of patients (39%) in group 1 who had sustained an anterior myocardial infarction compared with groups 2 and 3 (29% and 20%, respectively), reflecting the higher incidence of early complications in patients with anterior myocardial infarction.

TABLE 1 *Comparison of groups at 48 hours after admission to hospital*

| | *Group 1* | *Group 2* | *Group 3* | *Group 4* |
|---|---|---|---|---|
| Patients scanned | 63 | 84 | 62 | 57 |
| Mean age (y) | 59 ±9 | 56 ±9 | 55 ±7 | 56 ±9 |
| Men:Women | 58:5 | 74:10 | 53:9 | 47:10 |
| Mean duration of chest pain (h) | 7·0 ±11·0 | 7·7 ±12·3 | 6·6 ±10·6 | 6·9 ±10·3 |
| Site of infarction | | | | |
| Anterior | 40 | 29 | 20 | — |
| Inferior | 12 | 37 | 28 | — |
| Others | 11 | 18 | 14 | — |
| Mean max. AST ±SD | 251 ±25 | 151 ±99 | 146 ±109 | 33 ±29 |

TABLE 2 *Incidence of positive $^{125}$I-labelled fibrinogen scans*

| | *Group 1* | *Group 2* | *Group 3* | *Group 4* |
|---|---|---|---|---|
| Scan positive | 21 | 15 | 10 | 6 |
| Scan negative | 42 | 69 | 52 | 51 |
| % positive | 33 | 18 | 16 | 11 |

TABLE 3 *Comparison of active cigarette smokers with non-smokers*

| | *Cigarette smokers* | *Non-smokers* |
|---|---|---|
| Scan positive | 28 | 14 |
| Scan negative | 85 | 55 |
| % scan positive | 25 | 20 |

In group 1, 33 per cent of patients developed isotopic evidence of venous thrombosis compared with 18 per cent and 16 per cent in groups 2 and 3, respectively, and only 11 per cent in group 4 (Table 2). The higher frequency of isotopically diagnosed venous thrombosis in patients with complicated myocardial infarction (group 1) is statistically significant ($\chi^2=10{\cdot}4658$, $P<0{\cdot}05$). Within group 1 the mean day of mobilization of all patients was 6·3 days; the mean day of mobilization of the scan positive patients was 6·6 days; and the mean day of mobility of the scan negative patients was 6·1 days. The enhanced risk of venous thrombosis occurring in patients with a complicated myocardial infarction (group 1) was not selectively associated with any individual complication such as heart failure or arrhythmia.

Information on smoking habits was known in 229 patients but was not recorded in 37 (27 from groups 1, 2, and 3, and 10 from group 4). The number of active cigarette smokers in each of the groups of patients who suffered a proven myocardial infarction was similar (group 1 65%, group 2 63%, and group 3 59%), but was lower in the patients with chest pain not caused by myocardial infarction (group 4 45%). Examination of the combined groups of patients with a myocardial infarction failed to reveal a negative association between cigarette smoking and the development of deep venous thrombosis ($\chi^2=0{\cdot}2662$, $P>0{\cdot}5$) (Table 3).

This was true when cigarette smokers were compared with those people who had never smoked any form of tobacco ($\chi^2=2{\cdot}4893$, $P>0{\cdot}1$), or with persons who had previously smoked cigarettes or who were current pipe or cigar smokers ($\chi^2=0{\cdot}0269$, $P>0{\cdot}7$). Similarly, cigarette smoking did not protect against venous thrombosis in patients within each group, including group 4.

## Discussion

The results of this study indicate that the risk of developing deep venous thrombosis after myocardial infarction is related to the severity of the underlying illness rather than to the period of bed rest to which our patients were subjected. This is suggested by three facts. First there was a similar incidence of venous thrombosis in patients with uncomplicated myocardial infarction whether they were electively mobilized after two (group 2) or nine days (group 3). Second, within the group of patients with complicated myocardial infarction (group 1), the mean day of mobilization was virtually the same in those patients who developed venous thrombosis as in those who did not. Third, there was a higher incidence of venous thrombosis among group 1 patients than among those in group 3; put differently, more severely ill patients mobilized at 6·6 days had a significantly higher incidence of venous thrombosis (33%) than patients with an uncomplicated illness who were mobilized electively three days later (18%). These findings support the view of Nicolaides *et al.* (1971) that patients who are 'severely' ill are the most likely to develop venous thrombosis. However, in their study the duration of bed rest was not taken into account and the description of 'severely' ill was only applied to those patients who had a low output state for at least 24 hours. Many of the patients in our 'complicated' group would not have been classified as 'severely' ill by this criterion, and this probably accounts for the fact that Nicolaides *et al.* found a very high frequency of deep venous thrombosis (62%) in severely ill patients.

We have been unable to confirm that cigarette smokers with heart attacks develop deep venous thrombosis less frequently than non-smokers, and this finding is contrary to the observations of Marks and Emerson (1974). We were unable to collect information of smoking habits in 27 patients, but even if it were assumed that those with a positive scan (4 patients) were non-smokers and that all those with a negative scan (23 patients) were smokers, there was still no evidence of any protective effect from cigarette smoking.

We thank Professor J. R. A. Mitchell, Dr. S. A. Allison, Dr. M. Knapp, Dr. P. J. Toghill, and Dr. M. V. Wells for allowing us to study the patients under their care.

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# Transient atrial fibrillation after minor head injury

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*Two patients developed transient rapid atrial fibrillation after a blow on the head. There was no evidence of neurological damage or organic heart disease on subsequent investigation. Neither patient was aware of the cardiac irregularity.*

Atrial fibrillation most commonly results from organic heart disease but may occur in patients with clinically normal hearts (Friedlander and Levine, 1934). Sometimes in these cases it follows stressful insults and has been recorded after pain, a period of heavy smoking, or excessive drinking of alcohol. Cranial trauma appears to have induced the arrhythmia but in the few previous reports the injury was severe and intracranial haemorrhage sustained (Marks, 1956; Bonofiglio, Bugaro, and Pantaleoni, 1967; Palma *et al.*, 1971). The association of atrial fibrillation after trivial head injury has not been previously clearly recognized.

## Case reports

### Case 1

A fit 19-year-old man was being examined for entry into the forces. His heart was found to be normal. When the medical officer tried to look into his left ear with an auriscope he fell over and struck his head on a cupboard. He lost consciousness for about a minute and his pulse was rapid and irregular. He was sent to hospital where an electrocardiogram confirmed atrial fibrillation with a few ventricular ectopic beats. The patient at no time felt palpitation and was otherwise well. A chest *x*-ray film was normal. No treatment was given. On review, a week later, clinical examination of his heart and the electrocardiogram showed no abnormality.

### Case 2

A 32-year-old heavy labourer was admitted to hospital after a fight during which he had fallen over, struck his right forehead, and lost consciousness for a short time. On the evening of admission he had drunk 4 pints of beer. He had had no previous illness and was not a smoker. On examination there were no abnormal neurological signs but he had a fast and irregular heart beat. An electrocardiogram showed atrial fibrillation at a rate of 150 beats a minute. He was unaware of the arrhythmia. Twenty-four hours later he had reverted to sinus rhythm and his heart was normal on clinical examination. An electrocardiogram recorded at that time showed no abnormality. A chest *x*-ray film was normal and serum thyroxine was 114 nmol/l (normal range 70 to 160 nmol/l). The patient made an uneventful recovery.

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## Discussion

Both patients developed rapid atrial fibrillation after a blow to the head. Neither had primary cardiac disease. The fact that the development of the abnormal rhythm was noted and recorded directly after the cranial injury suggests that these events were related.

It is known that cerebral lesions may influence cardiac action. Electrocardiographic changes sometimes follow intracranial haemorrhage (Menon, 1964) and transient atrial fibrillation followed subarachnoid haemorrhage in 1 of 12 cases of this condition reported by Shuster (1960). The mechanism may be a reduction in the atrial refractory period mediated by vagal stimulation, as atrial premature beats can induce atrial fibrillation (Killip and Gault, 1965). This seems particularly likely to occur where simultaneous sympathetic overactivity also increases the heart rate. The blow on the skull in these patients may have induced such vagal and sympathetic excitation. In the first patient it is also possible that the manipulation of the auriscope in the external auditory meatus was the initiating factor. Fowler and Baldridge (1931) reported atrial fibrillation in a previously fit 24-

year-old medical student who fainted after removal of ear wax.

It is interesting that neither patient was aware of the rapid irregularity of the heart as this is usual in paroxysmal atrial fibrillation. It is possible that transient arrhythmias may not be uncommon after head injury.

I am grateful to Dr. D. W. Barritt, consultant physician, for his help and for allowing me to publish details of his patients.

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*British Heart Journal,* 1976, **38**, 986–989.

# Evaluation of rapid atrial pacing in diagnosis of coronary artery disease

## *Evaluation of atrial pacing test*

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*Seventeen patients presenting with anginal-type pain were studied by bicycle exercise testing, rapid atrial pacing, and coronary angiography. Ten patients with angina and abnormal pacing tests at rates less than 180/minute were found to have significant coronary artery disease as demonstrated by coronary angiography. Seven patients with pacing-inducea chest pain only at rates of 180 and above had normal coronary angiograms. This suggests that patients requiring rates of 180 or more to produce a positive atrial pacing test, following our protocol, do not usually have significant coronary artery disease though confirmation requires a larger study.*

Atrial pacing has proved to be a useful, reproducible test (Balcon *et al.,* 1969) in assessing myocardial function (Linhart, 1972), in order to enable myocardial lactate metabolism to be studied, providing objective evidence of myocardial ischaemia (Neill, 1968; Parker *et al.,* 1969; Forrester *et al.,* 1971), and in the diagnosis of ischaemic heart disease (Livesley and Oram, 1973), but does not correlate with coronary angiography as well as the angina-limited work load during progressive exercise testing (Bahler and MacLeod, 1971). To make the test more sensitive, Cokkinos *et al.* (1973) advocated the use of atropine, to enable a higher pacing rate to be used. Using atropine, we had seen a few patients in whom pacing at very fast rates produced evidence of ischaemia, but the exercise test and coronary angiogram were normal. To assess these findings further, we studied 17 patients, referred with a possible diagnosis of angina pectoris, by exercise and pacing tests, and then coronary angiography.

### Patients and methods

Seventeen patients were studied by exercise testing and atrial pacing to evaluate their presenting symptom of chest pain after informed consent was given for the pacing study, and coronary angiography was subsequently performed, to assess their suitability for coronary artery surgery. Two other patients with normal exercise and pacing tests up to 210/min were not considered to have sufficiently severe symptoms to warrant further investigation. No patients were receiving medication apart from, in some cases, β-blockers, which were stopped one week before investigation. The assessment of whether the pain was typical or atypical of angina pectoris was made prospectively by one of us (D. C. Fluck) on the basis of the patient's history, physical examination, chest *x*-ray film, and resting electrocardiogram.

### Exercise test

This was performed on one occasion on an Elema-Schönander bicycle ergometer. After being familiarized with the equipment, the patients were rested and then performed continuous multistage ergometry, starting at 25 Joules per second and increasing every minute by 25 Joules per second, until limited by fatigue, angina, ischaemic electrocardiographic abnormalities, or arrhythmias. Patients were monitored by bipolar transthoracic electrocardiograph leads, and a full standard electrocardiogram was recorded immediately after exercise. An ischaemic exercise electrocardiogram was defined as

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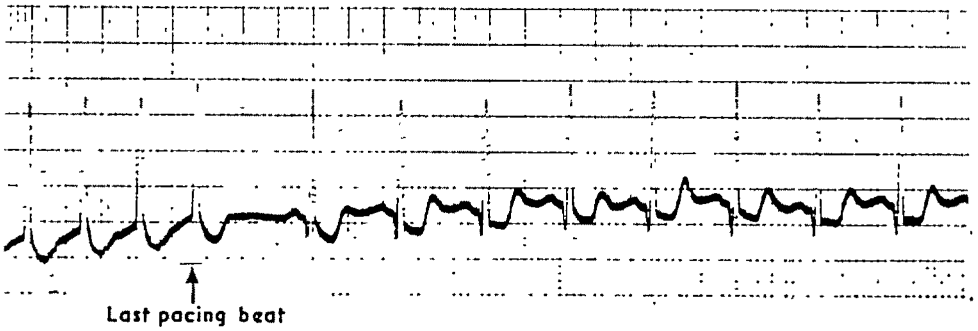

FIG. 1 *ST changes on stopping pacing associated with pacing induced chest pain (Case 4).*

one with horizontal ($< 1$ mV/s) or downsloping ST depression more than 0·1 mV, occurring 80 ms beyond the R wave, for five consecutive beats (Roitman, Jones, and Sheffield, 1970).

### Atrial pacing test

Catheterization was performed in the post-absorptive state after premedication with diazepam 5 mg orally 2½ hours before pacing, in all patients, as diazepam can increase myocardial blood flow (Ikram, Rubin, and Jewkes, 1973). A Zucker No. 6 or 7 bipolar pacing catheter was introduced into the mid-point of the main coronary sinus, and a No. 18 polyethylene catheter into the brachial artery. The position of the coronary sinus catheter was confirmed at the beginning and end of the study by the injection of contrast medium. Atropine 0·6 mg or 1·2 mg i.v. was administered 5 minutes before pacing. Pacing was begun using a Devices pacemaker at a rate of 20 beats/minute above the highest exercise heart rate obtained, or 160/minute, whichever was the less (Cases 10, 13, and 15 could only be paced at lower rates), and increased by 10 beats/minute every minute for 5 minutes, until limited by pain or the development of conduction block, when the rate was kept constant for the rest of the 5-minute period.

A bipolar transthoracic electrocardiographic lead was monitored throughout. We used pacing-induced chest pain, suggestive of angina pectoris, and similar to the patients' original pain, as our end-point (Kelemen *et al.,* 1973). ST depression, persisting after pacing was stopped, except for the first post-pacing beat (Parker *et al.,* 1969) (Fig. 1 and 2), was measured.

### Coronary cineangiography

This was subsequently performed, together with left ventriculography, by the Judkins technique. The degree of coronary artery narrowing was assessed independently (Dr. R. Pridie), each vessel being graded as: 0—normal; 1—plaque without significant narrowing ($< 50\%$); 2—50 to 70 per cent narrowing in area; 3—$>70$ per cent narrowing in area; 4—vessel occluded.

## **Results** (Tables 1 and 2)

### Group A

Seven patients required pacing up to 180 beats/minute or more to produce chest pain, associated with $>1$ mm ST depression in 6. All 7 patients had normal exercise electrocardiograms, but no significant coronary arterial lesions on angiography.

### Group B

All 10 patients had significant coronary arterial

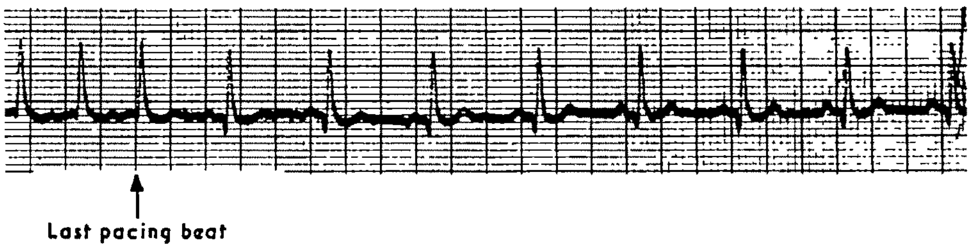

FIG. 2 *ST changes on stopping pacing in a patient in whom pain did not occur.*

TABLE 1 *Results of pacing and angiography: Group A*

| *Case No.* | *Sex* | *Age (y)* | *History* | *Exercise test* | *Pacing* | | | *Angiography* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Rate* | *Post-pacing ST-depression (mm)* | *Pain* | *LM* | *LAD* | *Cx* | *R* | *EF* |
| 1 | M | 39 | Atypical | — | 210 | 1·5 | + | 0 | 0 | 0 | 0 | 82·6 |
| 2 | M | 59 | Atypical | — | 180 | 1·5 | + | 0 | 0 | 0 | 0 | 71·1 |
| 3 | M | 23 | Atypical | — | 200 | 2 | + | 0 | 0 | 0 | 0 | 70·4 |
| 4 | F | 46 | Atypical | — | 180 | 2·5 | + | 0 | 0 | 0 | 0 | 87·0 |
| 5 | M | 36 | Angina | — | 190 | 1·5 | + | 0 | 0 | 0 | 0 | 67·1 |
| 6 | M | 53 | Angina | — | 180 | 1·5 | + | 0 | 1 | 1 | 0 | 67·6 |
| 7 | M | 46 | Atypical | — | 180 | 0 | + | 0 | 1 | 0 | 0 | 69 |

*Abbreviations:* LM=left main coronary artery; LAD=left anterior descending coronary artery; Cx=circumflex coronary artery; R=right coronary artery; and EF=ejection fraction.

TABLE 2 *Results of pacing and angiography: Group B*

| *Case No.* | *Sex* | *Age (y)* | *History* | *Exercise test* | *Pacing* | | | *Angiography* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Rate* | *Post-pacing ST-depression (mm)* | *Pain* | *LM* | *LAD* | *Cx* | *R* | *EF* |
| 8 | M | 53 | Angina | + | 130 | 0·5 | + | 0 | 3 | 3 | 4 | 67·4 |
| 9 | M | 54 | Angina | — | 150 | 0·5 | + | 0 | 3 | 1 | 0 | 81·2 |
| 10 | M | 56 | Angina | — | 150 | 1·5 | + | 0 | 4 | 1 | 2 | 83·1 |
| 11 | M | 50 | Angina | + | 120 | 1 | + | 1 | 3 | 2 | 1 | 76·1 |
| 12 | M | 53 | Angina | + | 170 | 1 | — | 0 | 3 | 2 | 3 | 62·5 |
| 13 | M | 57 | Angina | + | 145 | 2 | + | 3 | 1 | 2 | 4 | 65·2 |
| 14 | M | 57 | Angina | + | 170 | 2 | + | 0 | 4 | 2 | 4 | 61·1 |
| 15 | M | 56 | Angina | + | 140 | 4 | + | 0 | 3 | 3 | 4 | 42·6 |
| 16 | M | 64 | Angina | + | 140 | | + | 0 | 3 | 3 | 3 | 67·4 |
| 17 | M | 55 | Angina | — | 150 | 3 | + | 0 | 1 | 4 | 4 | 70 |

*Abbreviations:* LM=left main coronary artery; LAD=left anterior descending coronary artery; Cx=circumflex coronary artery; R=right coronary artery; EF=ejection fraction.

lesions on angiography, 9 of whom had pacing induced angina at rates < 180 beats/minute. Seven patients had ischaemic electrocardiographic abnormalities on exercise.

## Discussion

When the atrial pacing test was first introduced (Sowton *et al.*, 1967), pacing up to 160/minute was used. Increasing the pacing rate further is often possible after intravenous atropine, even to ≥200/minute, as described by Cokkinos *et al.* (1973), who advocated pacing at these fast rates to increase the sensitivity of the test. However, at these faster, sometimes unphysiological rates, not only is the oxygen consumption of the heart increased, but shortening diastole can decrease coronary blood flow (Knoebel *et al.*, 1970; Corday *et al.*, 1959) both directly by decreasing the time during which coronary blood flow occurs (Laszt and Muller, 1957; Gorlin, 1966), and indirectly by decreasing cardiac output, as a result of the decreased diastolic filling time of the heart (Corday and Lange, 1966). Furthermore, rates of this level are rarely achieved in maximal exertion. Hence, it is conceivable that ischaemia could be produced in normal hearts if the heart is paced sufficiently fast.

In our 17 patients, the 7 who required pacing up to 180/minute or more to precipitate angina-like pain, had normal coronary angiograms, left ventriculograms, and had normal exercise electrocardiograms. Thus, with our protocol, an angina-limited pacing rate of 180/min appears to differentiate between patients with normal coronary arteries, who can be paced up to this rate, or higher, before developing angina and hence do not require coronary arteriography, while those developing pain at lower pacing rates are likely to have coronary artery disease. In contrast, Cokkinos *et al.* (1973) reported 4 patients with chest pain at rates ≥180/minute, all subsequently shown to have abnormal coronary angiograms. However, all 4 had a positive double Master test. In addition, Walsh, Rickards, and Balcon (1975), reported 14 out of 50 patients, in which a negative pacing test was associated with coronary angiograms showing >75 per cent narrowing in at least one coronary artery. These findings could be the result of differences in the pacing protocols; the importance of exercise protocols has been thoroughly investigated, in particular, a rapid increase in work load results in angina at a higher triple product (of heart rate, systolic pressure, and ejection time) than if the increase is more gradual, producing angina after three minutes exercise (Redwood *et al.*, 1971), stressing the importance of using identical pacing protocols when studies are compared.

Although it is possible that pacing at rates of 180/minute or more could produce ischaemia in normal hearts, some patients with normal coronary angiograms do have angina at rates of 150 or less (Kemp *et al.*, 1973). Some of our patients with normal coronary angiograms and pacing-induced angina may belong to this group and have an abnormal myocardium (Richardson *et al.*, 1974), but we suggest that myocardial ischaemia may also occur in normal hearts if stressed sufficiently.

Coronary angiography was performed in the Cardiac Department, Harefield Hospital by arrangement with Dr. M. K. Towers.

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# Case reports

*British Heart Journal*, 1976, **38**, 990–992.

# Giant blood cyst of tricuspid valve
## *Successful excision in an infant*

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*A case of a giant blood-filled cyst of the tricuspid valve is described in a 4-month-old infant. The cyst caused obstruction of the right ventricular inflow and outflow tracts and a right-to-left shunt; it was successfully removed at open heart surgery. Pitfalls in differential diagnosis and the pathogenesis are discussed.*

Cardiac tumours in infancy are exceedingly rare, particularly primary ones (Nadas and Ellison, 1968; Van der Hauwaert, 1971). Among these, to our knowledge, no case of symptomatic giant blood-filled cyst of the heart valves has been reported.

Small, pin-point cysts of the atrioventricular valves, usually multiple and located on the atrial surface of the leaflets, are a frequent finding at necropsy in infants under 6 months of age (Boyd, 1949).

The following case report is concerned with a 4-month-old infant who was successfully operated upon in our hospital for removal of a giant cyst of the tricuspid valve.

## Case report

A 4-month-old baby girl, weighing 4·9 kg, was referred to the Cardiology Department by her family doctor with a generic diagnosis of congenital heart disease. At birth, she had difficulty in breathing. At 1 month of age, an increase in heart size associated with cyanosis at rest led to the referral diagnosis and she was treated with digitalis.

At admission she was a well-nourished and developed baby with no signs of distress. However, cyanosis of the finger nails and visible mucosae was present. Heart rate was 150 and regular; systolic blood pressure was 95 mmHg (12·6 kPa).

Examination of the heart revealed a right ventricular lift without thrills. The first heart sound at the apex was loud and widely split, the second was single and weak. There was an $S_4$ gallop and, at times, an $S_3+S_4$ slightly louder at the apex. A grade 2/6 short systolic regurgitant murmur was audible at the apex and at the left of the sternum. The liver was barely palpable below the right costal margin.

The haemoglobin level was 13·5 g/dl, haematocrit 52 per cent, and white blood count 11 200/mm$^3$.

Chest *x*-ray examination showed moderate cardiomegaly, with reduced pulmonary vascular markings. The electrocardiogram showed sinus tachycardia, the QRS axis at +80 degrees, and right atrial and ventricular hypertrophy.

During cardiac catheterization, blood oxygen saturations were determined in the right and left heart chambers, and revealed obvious desaturation in the right atrium and ventricle, and a right-to-left shunt through a patent foramen ovale (left atrial saturation 42%). Right atrial pressure was 8 mmHg (1·1 kPa), left atrial pressure 7 mmHg (0·9 kPa); right ventricular pressure was reduced to 11/0–2 mmHg (1·5/0–0·3 kPa). The catheter could not be passed into the pulmonary artery.

On cineangiocardiography, the contrast media, injected into the right ventricle, showed the cavity to be partially occupied by a bean-like mass, freely moving up and down through the tricuspid valve, probably connected to its septal leaflet (Fig. a). Regurgitant flow into the right atrium promptly visualized the left heart cavities and the aorta. The mass was clearly visible when contrast medium was injected directly into the right atrium (Fig. b). Forward flow slowly passed through an apparently rigid pulmonary valve. The final diagnosis was a right atrial mass. Surgical intervention was recommended.

The heart was explored through a median sternotomy and normothermic total cardiopulmonary bypass. The right atrium was filled by a bluish, smooth mass extending through the tricuspid valve into the right ventricle and attached to the septal leaflet by a thin, 5 mm long pedicle. The mass was removed with its valvular insertion, which was repaired by suture.

Macroscopical examination of the tumour disclosed a unilocular cyst, 3 × 2 cm, filled with blood and with fibrin layers on the inner surface. The cystic wall was 1 mm thick and its histological examination showed oedematous connective tissue rich in fibroblasts and collagenous bands and scarce in ground substance. No elastic fibres were shown by Weigert staining. Both the inner and outer sides of the wall were lined with a thin endothelium. The cyst pedicle had a central lumen through which the cavity communicated with the right ventricle.

The patient's recovery was uneventful. At follow-up after 2 years, the child was active and developing normally; her heart size was much reduced and the electrocardiogram was within normal limits.

## Discussion

Despite an exhaustive search, no reports of symptomatic giant cyst of the tricuspid valve with diagnosis during infancy and successful removal were found, even though the high postmortem incidence of small blood cysts of the heart valves in infants is well documented. There are a few reports of large cysts of heart valves in children of school age and in young adults (Liese, Brainard, and Goto, 1963; Cumming and Ferguson, 1965; Sakakibara *et al.*, 1967; Leatherman *et al.*, 1968). These cysts, which caused more or less severe symptoms of valvular stenosis, were correctly diagnosed and surgically removed from the pulmonary valve in three instances (Liese *et al.*, 1963; Cumming and Ferguson, 1965; Sakakibara *et al.*, 1967), and the mitral valve in one (Leatherman *et al.*, 1968).

In our case, the cyst cavity was unilocular, filled with blood, and lined with endothelium. It communicated through a fine pedicle, implanted on the atrial side of septal leaflet of the tricuspid valve, with the cavity of the right ventricle. This finding supports Boyd's pathogenetic theory that these cysts are formed by blood pressed into crevices on the ventricular surface of the valves, with subsequent sealing off of the portal of entry (Boyd, 1949). However, the size of the mass we observed and the absence of elastic fibres in its walls suggest that the cyst originated more like a diverticulum of the septal tricuspid leaflet, most probably as a result of a localized structural defect. On the other hand, the existence of a multiloculated haematic cyst with fibroelastic elements in the stroma (Cumming and Ferguson, 1965) and the finding of an intracardiac penduculated lymphangioma (Forel, 1919) lead us to speculate about a hamartomatous pathogenesis in these cases.

Another interesting point in our patient was the preoperative differential diagnosis. Some of the more

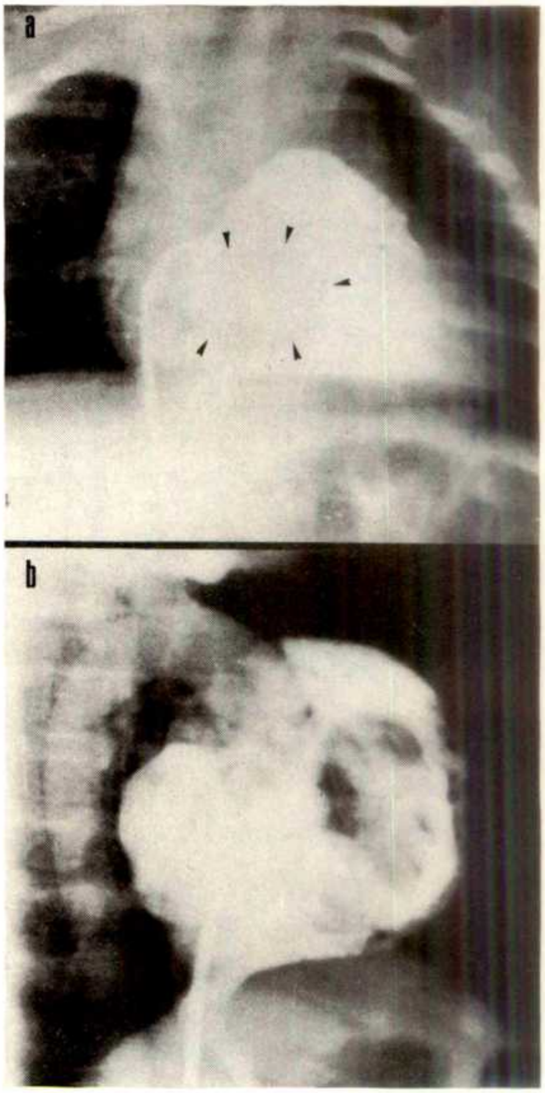

FIG. *a) Selective right ventricular angiogram (AP projection, early phase), showing a bean-like filling defect (between arrows), partially occupying the right atrial and ventricular cavities. b) Selective right atrial injection (lateral projection). Late diastole: the mass extends also to the proximal outflow portion of the right ventricle. A right-to-left shunt is present at the atrial level which visualized the left heart structures.*

impressive clinical findings, such as the cyanosis, early heart failure, and triple and sometimes quadruple rhythm associated with a systolic murmur, would have led us to suspect an Ebstein anomaly or a pedunculated intracavitary tumour. However, the relatively small size of the heart and electrocardiographic pattern of right ventricular hypertrophy were against the first, while the extreme rarity of intracavitary tumours in children under 4 years of age and the absence of conduction disturbances excluded the second possibility. The patient's symptoms and clinical findings were clarified by angiocardiographic demonstration of a mass moving through the tricuspid valve, following the excursions of its septal leaflet and obstructing both the right ventricular inflow and outflow.

Surgical removal of the mass has proved to be effective treatment for this child whose clinical course has since been uneventful.

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# Cervical aortic arch and a new type of double aortic arch
## *Report of a case*

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*A case of cervical aortic arch is reported. To the best of our knowledge, it is the first to be associated with a serious intracardiac anomaly. In addition, it is part of a new type of double aortic arch, caused by failure of reabsorption of both dorsal aortic roots and persistence of the fourth right and second (or third) left branchial arches.*

Cervical aortic arch is a rare anomaly. A review of world publications shows only 17 reported cases (Beavan and Fatti, 1947; Bender, Menges, and Shulze, 1964; Chang *et al.*, 1971; Defrenne and Verney, 1968; De Jong and Klinkhamer, 1969; DuBrow *et al.*, 1974; Gravier, Vialtel, and Pinet, 1959; Harley, 1959; Hastreiter, D'Cruz, and Cantez 1966; Mahoney and Manning, 1964; Massumi, Wiener, and Charif, 1963; Mullins, Gillete, and McNamara, 1973; Pitzus and Camoglio, 1974; Richie *et al.*, 1972; Sheperd, Kerth, and Rosenthal, 1969; Shuford *et al.*, 1972). Right-sided in the majority of instances, it has been found only as an isolated entity. The purpose of this article is to describe a case associated with pseudotruncus and which constitutes a new type of asymptomatic double aortic arch.

## Case report

A 33-month-old undernourished male child,cyanotic since the age of 1 month, with a history of several upper respiratory infections was admitt3d for evaluation. Pertinent *physical findings* were a systolic thrill over the left supraclavicular region and a superficial venous network over face, neck, and upper trunk. Peripheral pulses were normal. Laboratory studies were within normal limits except for haematocrit (63%) and haemoglobin (17·3 g/100 ml). Electrocardiogram showed obvious right axis deviation, right atrial overload, pronounced right ventricular hypertrophy, and systolic overload. Phonocardiogram showed a modest systolic murmur at the second and third interspaces and an increased second heart sound. On chest *x*-ray film the heart was slightly enlarged; the apex was rounded and tilted upward. The pulmonary artery segment was concave and the hilar and pulmonary vascular markings were decreased. In the left anterior oblique projection the aortic knob was unusually high and prominent. Lungs were clear. At cardiac catheterization very low oxygen saturation values were found both in the venous (34·8% in right atrium) and arterial systems (38·9% in ascending aorta). The pulmonary artery could not be entered. The right ventricular pressure was 85/3–5 mmHg (11·3/0·4–0·7 kPa).

### Cineangiocardiogram

The right infundibulum wrs atretic. A dilated ascending aorta overrode a large ventricular septal defect. The aortic arch was right-sided. The first aortic branch crossed the midline, ascended to the left side of the neck, then turned abruptly downward and rejoined the aorta at the level of the right-sided arch. The second and third branches were, respectively, the right subclavian and right common carotid arteries. The left brachiocephalic arteries could not be properly assessed, but the left common carotid artery seemed to arise from the descending portion of the left cervical arch. A hypoplastic main pulmonary artery was supplied by a small persistent ductus arteriosus which originated from the

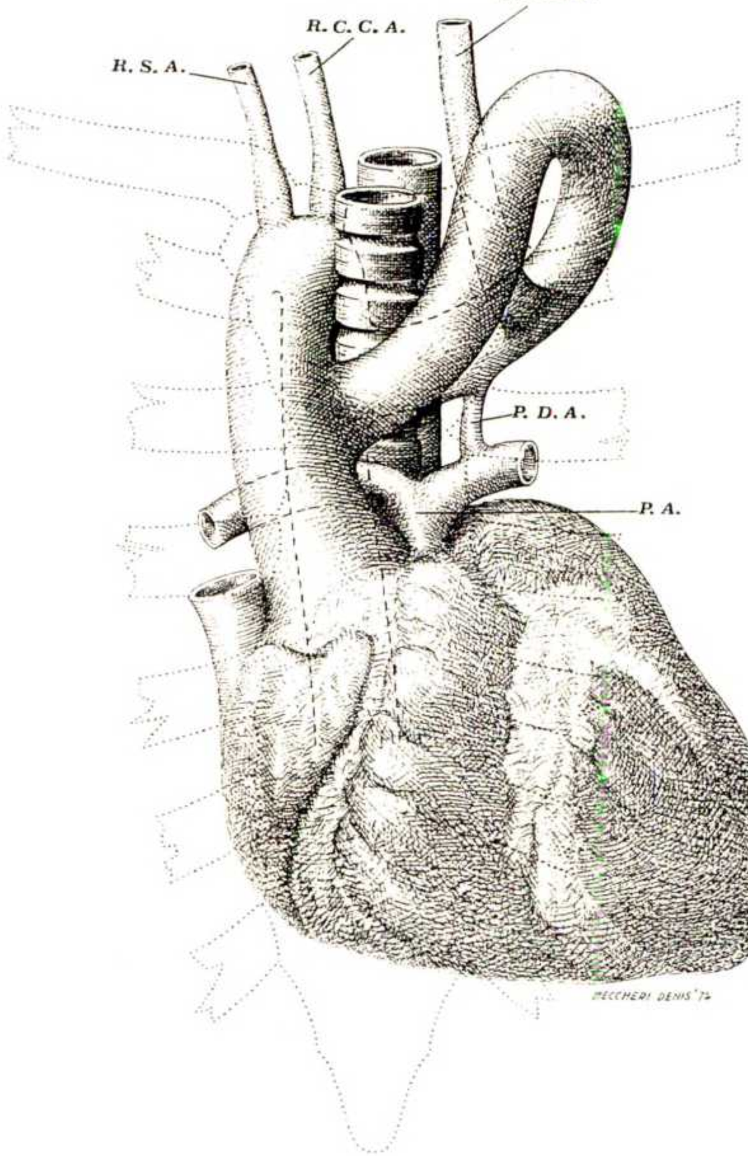

FIG. *Artist's representation showing the double aortic arch; left common carotid artery (LCCA); right common carotid artery (RCCA); right subclavian artery (RSA); pulmonary artery (PA); persistent ductus arteriosus (PDA).*

posterior portion of the cervical aortic arch. The thoracic aorta descended obliquely to the right of the spine and crossed the midline at the level of the diaphragm. Diagnosis was: pseudotruncus, hypoplastic pulmonary artery and branches supplied by a left persistent ductus arteriosus, right aortic arch, and left cervical aortic arch (Fig.). The child was discharged and no treatment was planned.

## Discussion

Double aortic arch and cervical aortic arch are developmental defects of the primordial branchial arches.

### Double aortic arch

As a rule, the double aortic arch results from persistence of both right and left fourth branchial arches. Usually the arches are at the same level, the right one being, at most, slightly higher. In our case the arches are at different levels. According to Edward's hypothetical double aortic arch (Stewart, Kinkaid, and Edwards, 1964), the malformation can be explained by failure of reabsorption of both dorsal aortic roots and persistence of the fourth right and second (or third) left branchial arches. The vascular ring results from the following structures: on the right, the ascending aorta proper and the right arch; anteriorly, the ascending portion of the cervical arch; on the left and posteriorly, the left cervical arch connecting with the right-sided thoracic aorta. The small persistent ductus arteriosus has no bearing in the formation of the ring.

Double aortic arch is usually suspected because of symptoms related to compression upon trachea and/or oesophagus. Our case had no symptoms because the ring was not encroaching upon these structures. In the majority of cases the diagnosis is easily made with angiography.

### Cervical aortic arch

The origin of cervical aortic arch is still controversial. One theory (Lewis and Rogers, 1953) holds that it is caused by retention of the fourth branchial arch at the cervical level. According to another theory (Beavan and Fatti, 1947; Harley, 1959; Lewis and Rogers, 1953; Mahoney and Manning, 1964) it derives directly from the third or second branchial arch. The controversy has been extensively explored by Shuford *et al.* (1972), who have shown that both hypotheses are equally valid. The first theory cannot explain the coexistence of a right thoracic arch with a left cervical arch in our case. One would have to assume a normal descent of the fourth arch on the right and a retention in the cervical region of the same arch on the left. A differential origin of the two arches, the right from the fourth and the left from the third (or second arch) is more likely.

The cervical aortic arch is usually asymptomatic, but symptoms related to compression of vital structures, such as stridor, dyspnoea, dysphagia, and frequent upper respiratory infections can be encountered. In a patient with a pulsating cervical mass the correct diagnosis can be suspected clinically and further substantiated by the disappearance of femoral pulses upon compression of the mass. A chest film may show a prominence or an abnormal knob on the left (or right) superior mediastinum. A mediastinal widening can be the only radiological finding. In some cases, however, the trachea is slightly displaced and compressed; in others, a barium study might show a posterolateral filling defect in the oesophagus, very similar to that occurring with an aberrant subclavian artery. Radiologically the differential diagnosis includes aortic diverticulum, aneurysmal dilatation of the aortic arch and/or branches, neurinoma, goitre, pulsion oesophageal diverticulum, buckling of the innominate artery, upper lobe atelectasis, dilatation of the superior vena cava, and aberrant right subclavian artery. Only angiography makes diagnosis possible. The contrast medium should be injected into the left ventricle or above the aortic valve. The ascending aorta, elongated and usually of normal size, reaches the supraclavicular region whence it turns abruptly downward. The aortic branches may be irregular in their distribution, but follow a well-defined embryological pattern. The descending aorta crosses the midline if the thoracic aorta is controlateral to the cervical arch.

Typically, the overall appearance has been compared to a hair-pin loop (Shuford *et al.*, 1972).

We wish to express our gratitude to Dr. Sergio Eufrate for critically reviewing the article.

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Requests for reprints to Dr. Mario Cornali, Ospedale Generale Provinciale, 54100 Massa, Italy.

# Correspondence

*British Heart Journal*, 1976, **38**, 997–998.

## Sudden cardiac death

Sir,

Drs. A. Myers and H. A. Dewar recently reported 100 cases of sudden cardiac death with coroner's necropsies in Newcastle upon Tyne and stated that 'the place of mobile coronary care units in preventing these deaths is clearly limited' *(British Heart Journal* (1975), **37**, 1133). We think that this is a laconic dismissal of an important development which is clearly shown to save patients who have experienced sudden cardiac death, a common cardiac event as the authors have pointed out. Perhaps the authors are right concerning mobile coronary care units with inordinate response times in cities without emergency medical systems incorporating lay training in cardiopulmonary resuscitation. However, our experience has certainly been different in a city of equivalent population to that of Newcastle upon Tyne.

Tampa, Florida, has a population of 300 000. The Rescue Division of the Tampa Fire Department has been providing paramedical service with five units since July 1972. Rescue response time is generally 3 to 5 minutes. The paramedics received their advanced training under the auspices of the Hillsborough County Medical Association and have a strong continuing education programme. These paramedics perform basic and advanced cardiopulmonary resuscitation, including defibrillation, telemetry, intubation (both tracheal and oesophageal), establish an intravenous route, and administer medication (both intravenous and intracardiac), as directed by a physician via radio contact. Electrocardiograms are interpreted by the paramedics on the scene as well as by a coronary care nurse at a hospital base station. Patients are transported to area medical facilities for further care by their personal physician.

Sudden cardiac death was defined for this study as a rapid, unexpected deterioration of vital signs in an individual who was going about his normal activities. Successful resuscitation was defined as treatment at the scene, admission and continued treatment at a hospital with eventual discharge.

From July 1974 to July 1975, resuscitation was attempted on 296 people found in ventricular fibrillation. The number of these fitting the criteria for sudden cardiac death is unknown. However, 34 who fulfilled the criteria for sudden cardiac death were successfully resuscitated. Out of the 296 people, an additional 34 people who did not fulfil the criteria for sudden cardiac death were successfully resuscitated, giving a 23 per cent overall successful resuscitation rate. This is similar to data reported from the mobile coronary care system in Seattle, Washington (Cobb and Alvarez, 1974).

This dramatic increase in survival from fatal cardiac events equals that accomplished by the institution of hospital coronary care units.

Eric E. Harrison, Edward J. Straub,
and Brent D. Amey,
The Cardiology Center,
Tampa General Hospital,
Tampa, Florida, USA.

### Reference

Cobb, L. A., and Alvarez, H. (1974). Medic I: the Seattle system for the management of out-of-hospital emergencies. Personal communication.

This letter was shown to Dr. H. A. Dewar and his co-author who reply as follows:

Sir,

The letter from Dr. Harrison and his colleagues has been passed on to us and we accept that the quoted statement in the article by us was laconic. But it was not inaccurate. We entirely agree with them that the results of a mobile coronary care service manned by paramedical personnel such as they describe, and whose counterpart in the U.K. is that pioneered in Brighton by D. A. Chamberlain and his helpers, are superior to those obtained when doctors alone are primarily involved. In Newcastle one of us (H.A.D.) had hoped shortly to supplement the doctor-manned service (which has been operating in the city since 1968) with specially trained ambulance men who ought to reach cases very much more quickly, but this improvement has been blocked by the Dept. of Health and Social Security.

Nevertheless in their letter Dr. Harrison and his colleagues show that in Tampa only 23 per cent of the patients with ventricular fibrillation upon whom resuscitation was attempted had a successful outcome. It is surely not inaccurate to describe such a success as 'limited'—however much one may admire it, as we indeed do. To save the 77 out of every 100 who died, a different approach from that of mobile coronary care is needed. It is arguable that the total disappearance of the habit of cigarette smoking for example might save more lives than any coronary care unit whether mobile or stationary.

A. Myers and H. A. Dewar,
The Royal Victoria Infirmary,
Newcastle upon Tyne.

---

## Erratum

In the paper 'The Natural History of rheumatic, aortic regurgitation and indications for surgery', which appeared on pp 147–154, line 19, p. 147, column 2 should read—'Fifty-three patients with moderate aortic regurgitation and 67 patients with moderate or severe aortic regurgitation of non-rheumatic aetiology referred during the same period were also excluded from the study'.

# *Correspondence*

*British Heart Journal,* 1976, **38,** 999–1000.

# Localization of lesion in patients with idiopathic orthostatic hypotension

Sir:

Idiopathic orthostatic hypotension is a fascinating condition and it is certainly important to localize the lesion. The author (Ibrahim, M. M. (1975), *British Heart Journal,* **37,** 868) is justified by his evidence in concluding that the lesion is probably somewhere in efferent sympathetic pathways. The trouble is that the paper produces a powerful *déjà vu* phenomenon. Johnson *et al.* (1966) reported patients in whom similar tests were done with similar conclusions, and in whom a fall-out of cells in the intermediolateral column was found at necropsy. This finding is compatible with degeneration of cell bodies of preganglionic cells. Since then other papers have supported this view and added further evidence. Among these are Vanderhaeghen, Perier and Sternon (1970), Bannister (1971), and Bannister and Oppenheimer (1972).

The condition and its association with degeneration elsewhere in the nervous system, and the many reports on the subject are reviewed in the chapter on arterial hypotension in *'Disorders of the Autonomic Nervous System',* Johnson and Spalding (1974).

J. M. K. Spalding,
Department of Neurology,
The Radcliffe Infirmary,
Oxford.

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Vanderhaeghen, J-J., Perier, O., and Sternon, J. E. (1970). Pathological findings in idiopathic orthostatic hypotension. *Archives of Neurology,* **22,** 207.

---

This letter was shown to Dr. Ibrahim who replies as follows:

Sir:

I am aware of many of the pathological studies that showed evidence of degenerative changes in cell bodies of preganglionic cells as Dr. Spalding indicated in his letter. However, I wonder if Dr. Spalding is familiar with other pathological studies in patients with idiopathic orthostatic hypotension where no lesions were found in preganglionic cells or efferent sympathetic fibres (Lewis and Dunn, 1967) and lesions in afferent or central pathways were suggested (Bannister, Ardill, and Fentem, 1967). That the automatic defect may involve afferent baroreceptor impulses as well as efferent vasoconstrictor pathways with a reduction in vascular stores of norepinephrine was indicated by the studies of Abboud and Eckstein (1966). Love *et al.* (1971) using physiological tests similar to those in my study described patients with lesions in afferent autonomic fibres without involvement of efferent fibres. It is unwise to suggest that all patients with idiopathic orthostatic hypotension have an efferent sympathetic disease, and, therefore, it is unfair to mention that my paper produces a powerful *déjà vu* phenomenon. Furthermore, I believe that Dr. Spalding is not aware that one of the main objectives of my study was to provide a plan to investigate in a systematic way the different components of the baroreceptor reflex arc that can help to localize—on clinical grounds—the site of the lesion in other diseases of the autonomic nervous system.

M. Mohsen Ibrahim,
Department of Cardiology,
Cairo University,
1 El-Sherifein St.,
Cairo, Egypt.

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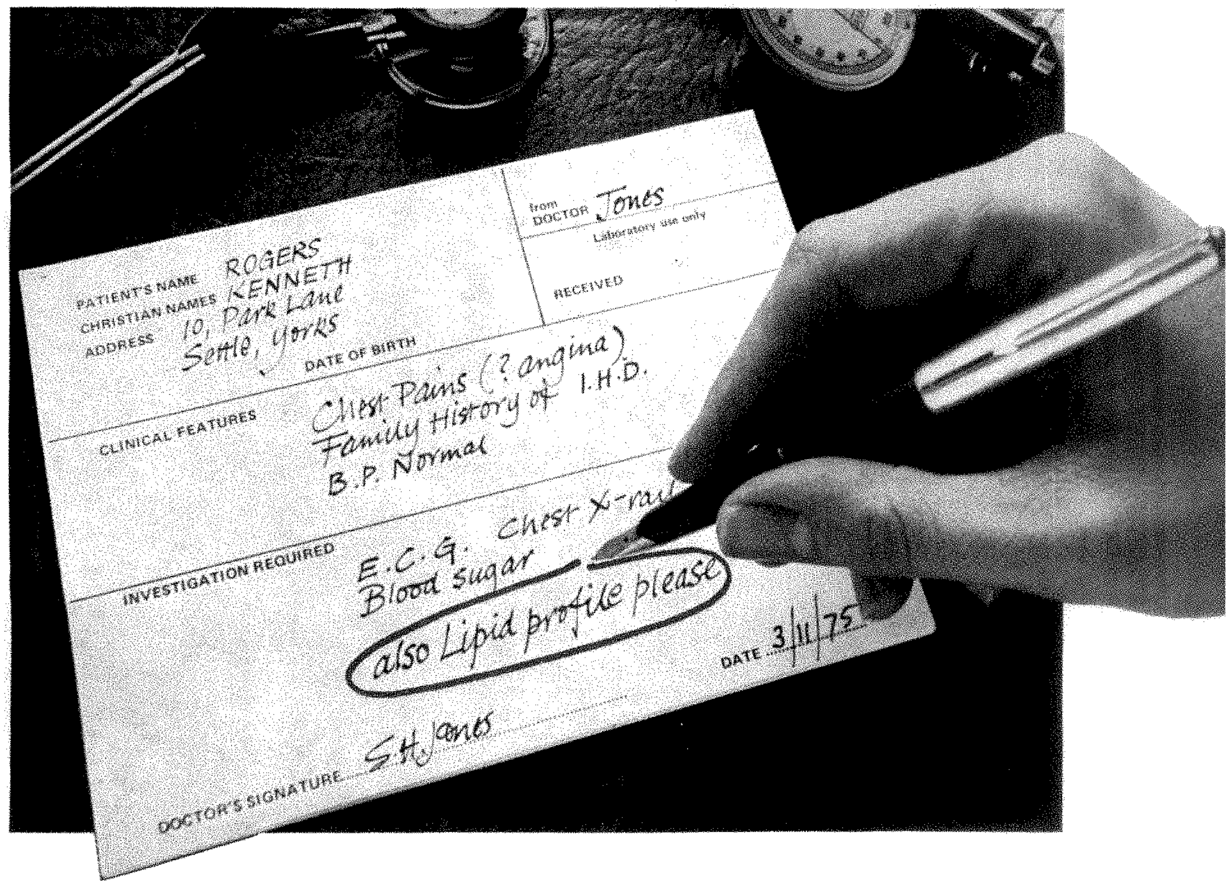

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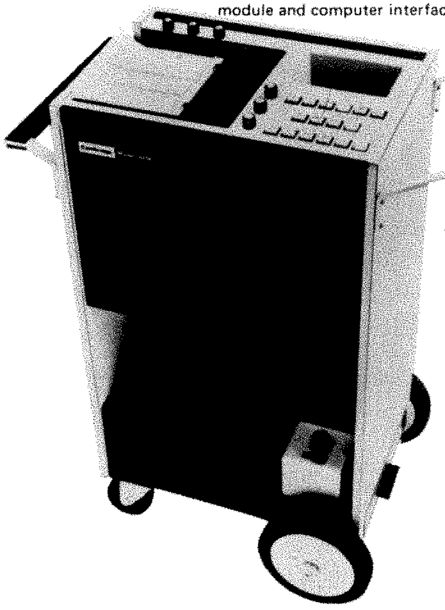

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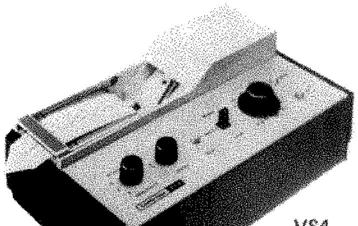

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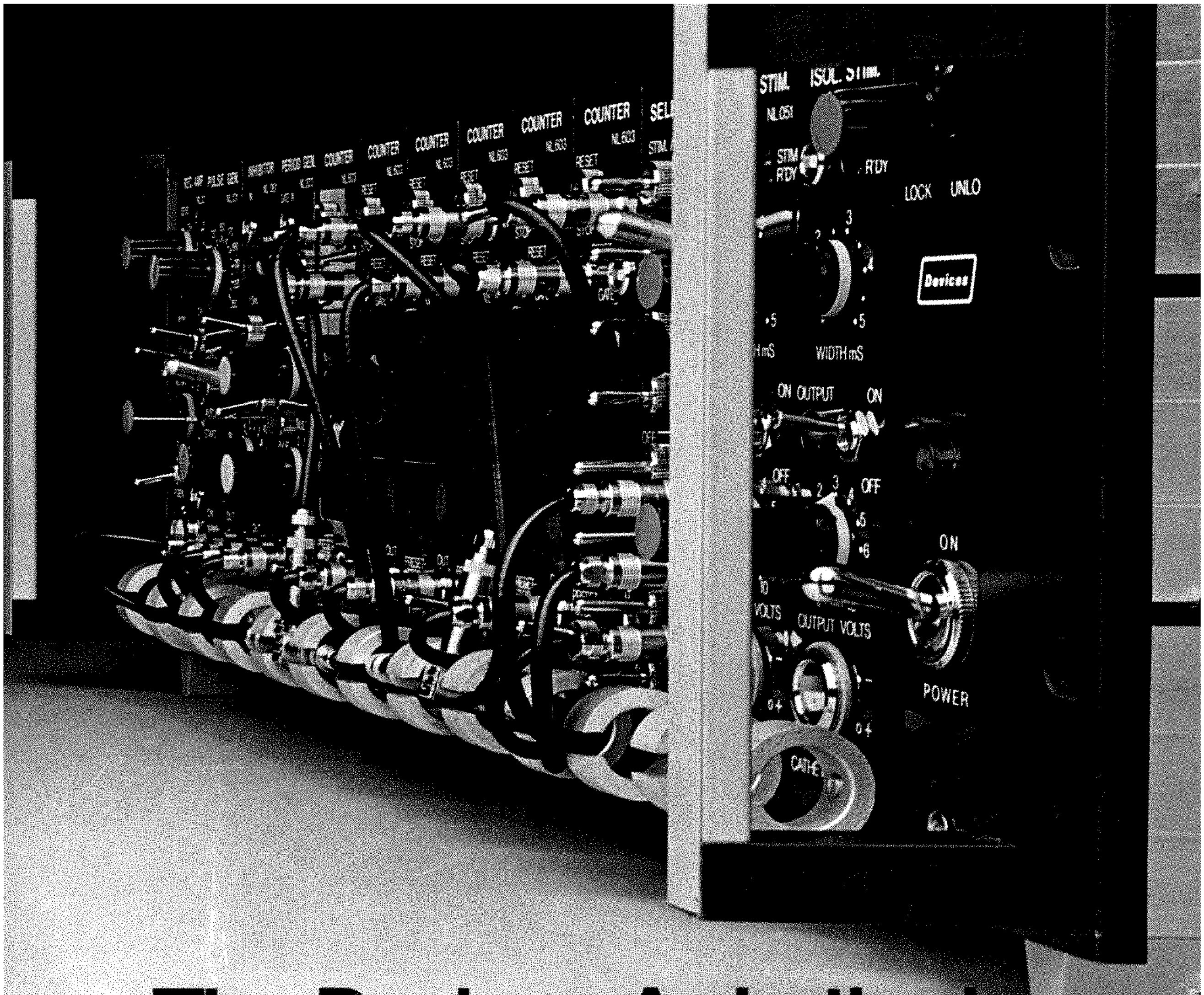

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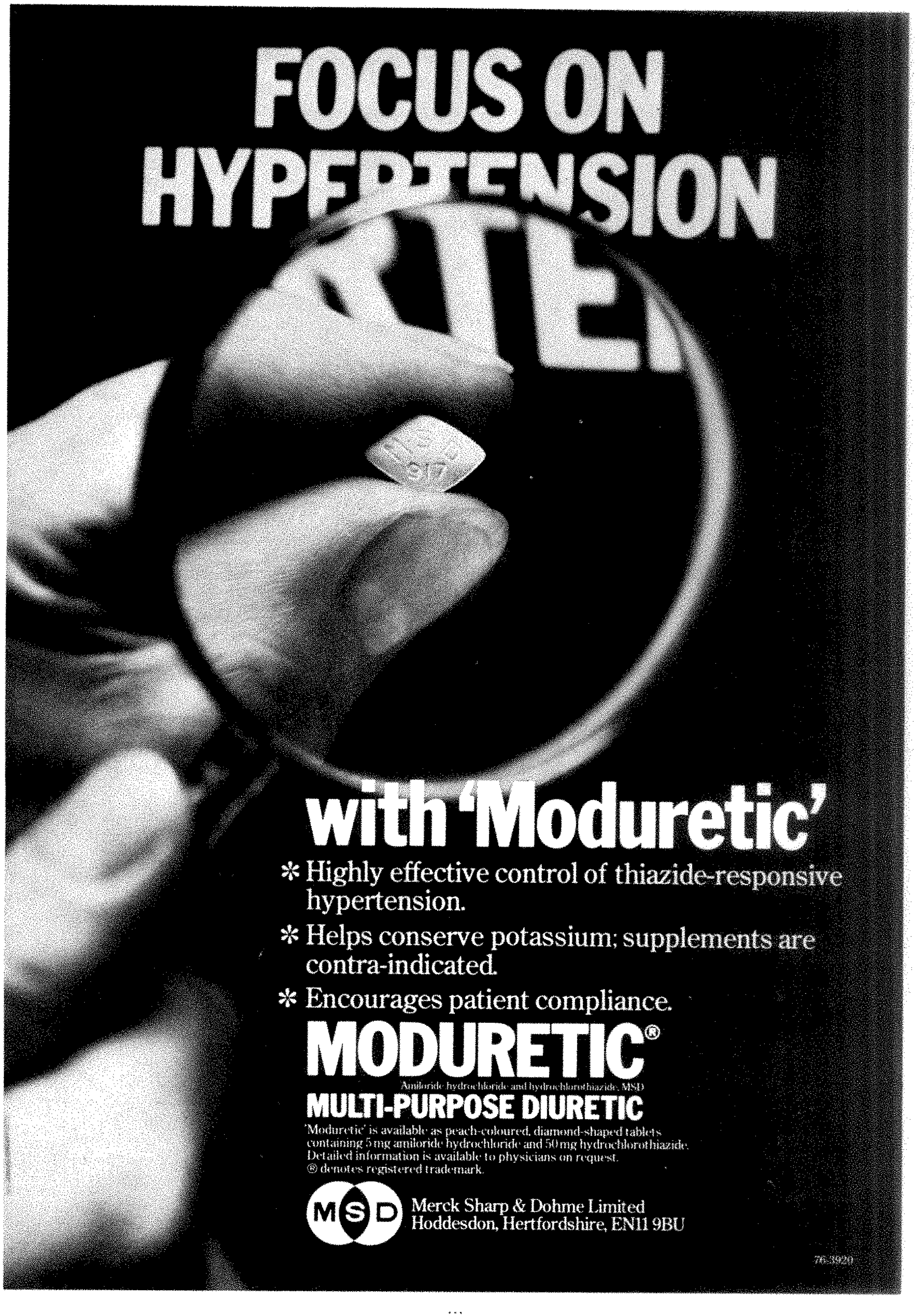

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The papers contained in this book were presented at the international symposium on "Diagnostic and Therapeutic Tools of Cardiac Pacing" in Munich. Current experience, new results, and future trends in this field are discussed in twenty-four summarized articles. Investigations of sinus node function, disturbances of AV conduction, and the electrophysiology of supraventricular and ventricular tachycardias receive special attention. The section on the sinus node includes new experimental and clinical data on sinus node automaticity and sinoatrial conduction properties. Recent advances in suction electrode recording are considered. The chapter on AV conduction covers the application of His bundle electrography with emphasis on conduction disturbances, AV-nodal tachycardias, preexcitation syndromes, and drug effects. The third part of the book is concerned with experimental, clinical, and electrocardiographic features of tachycardias. New pacing techniques to suppress supraventricular, junctional, and ventricular tachycardias are presented. Finally, the future of cardiac pacing is discussed.

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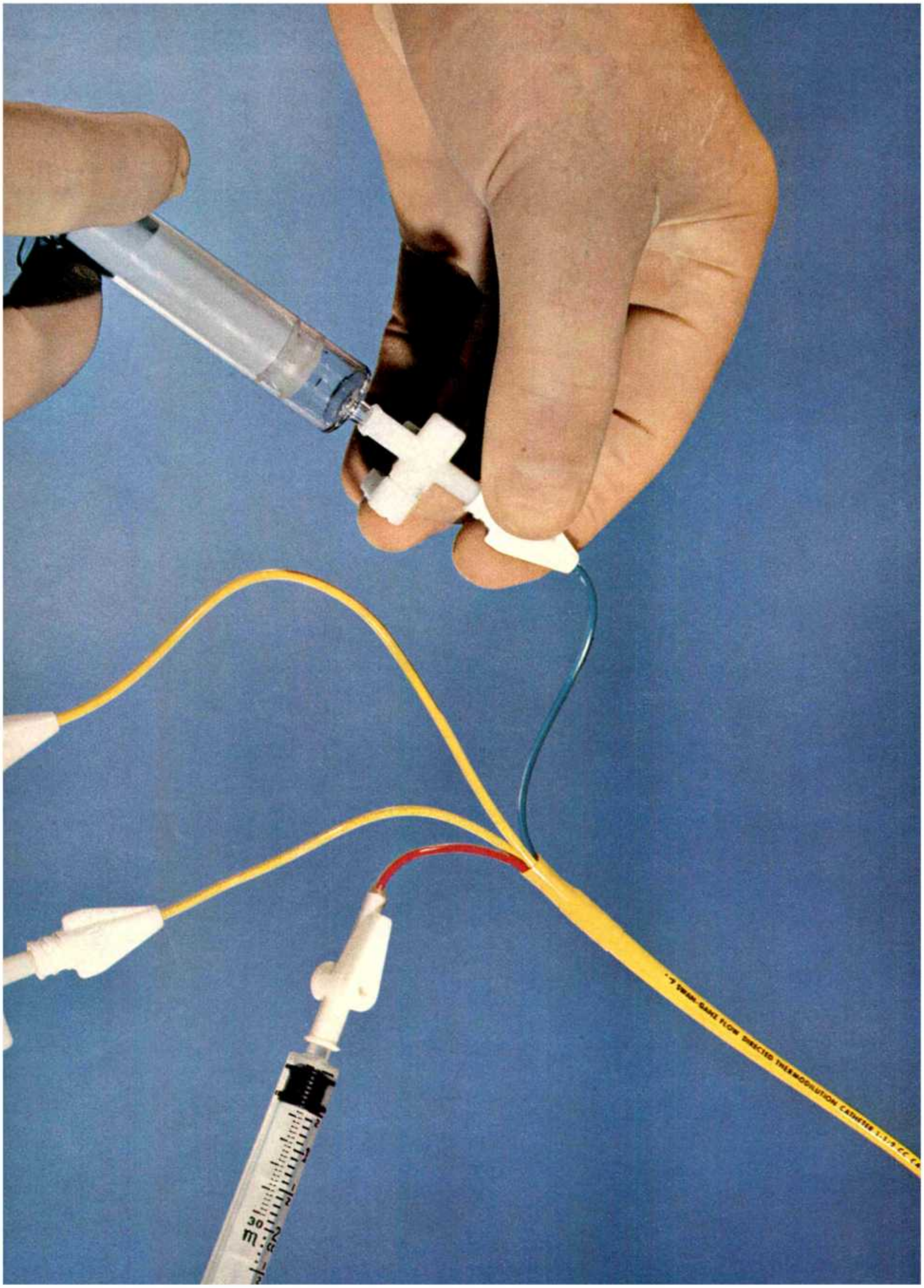
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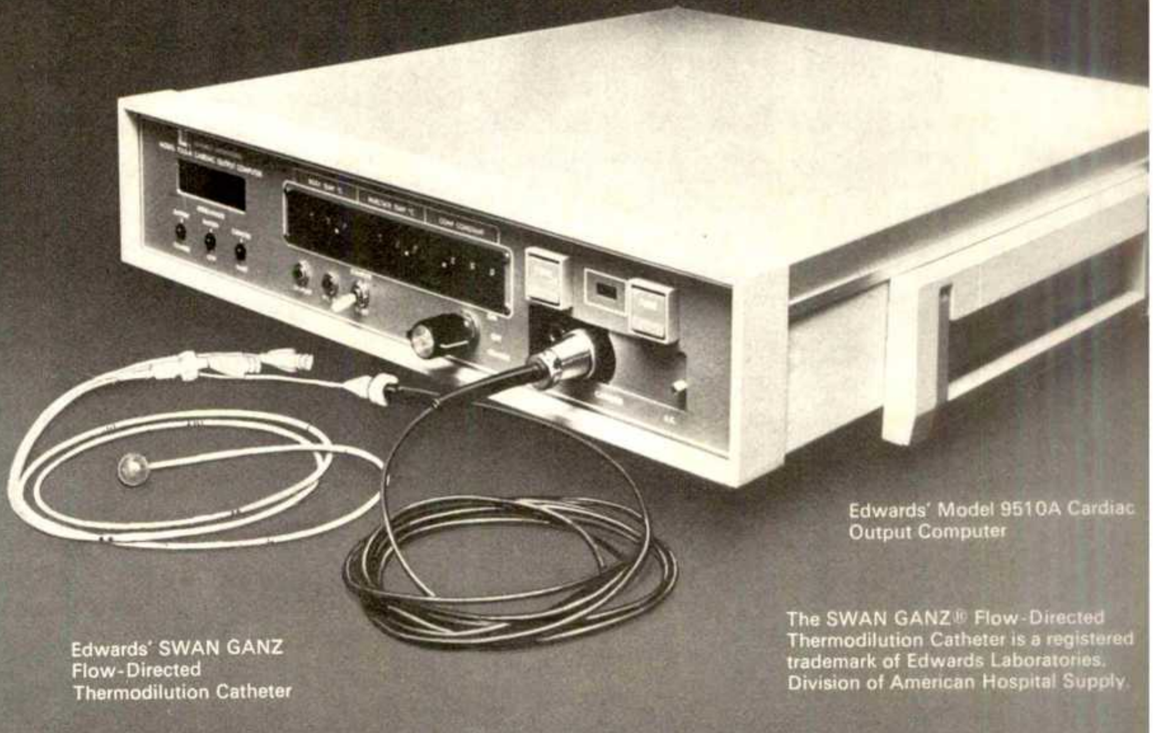

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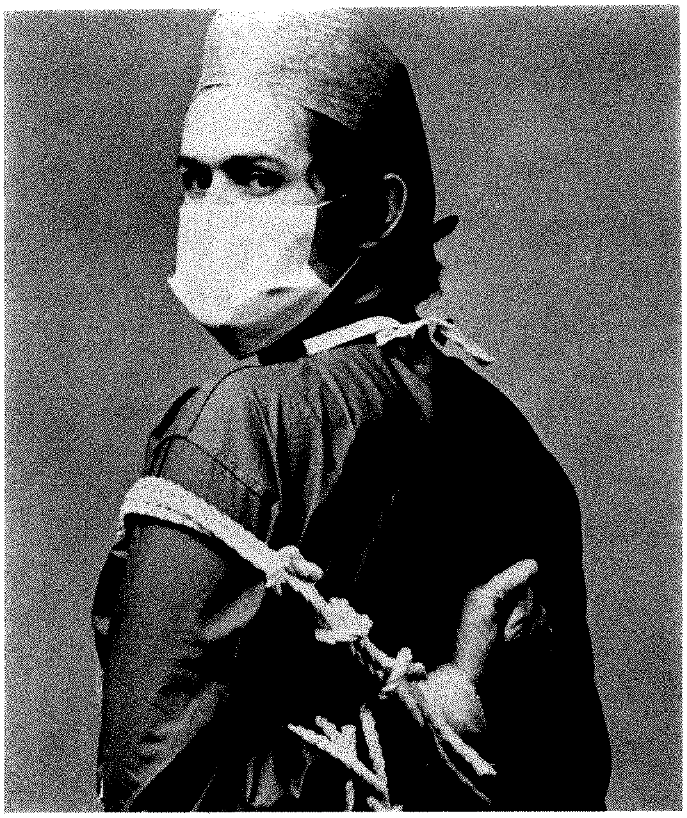

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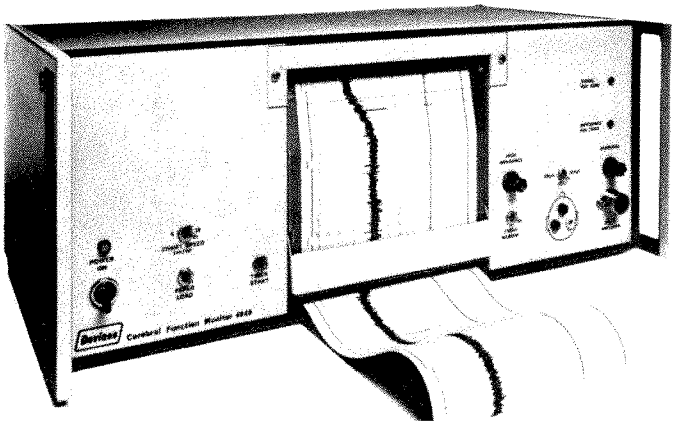

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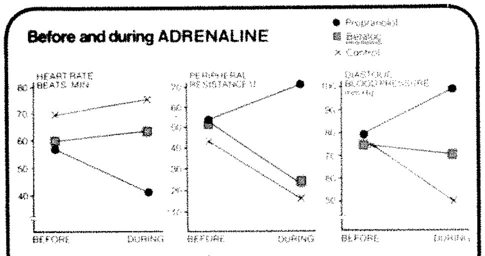

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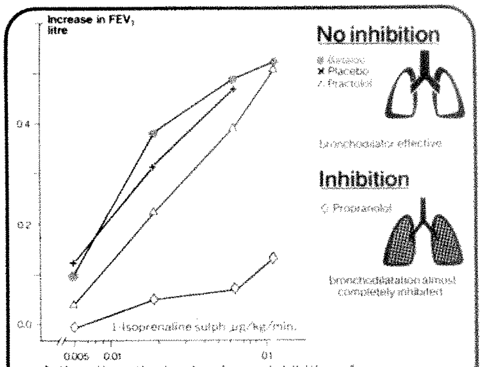

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1 (1975) *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 **University of Gothenburg, Sweden.**

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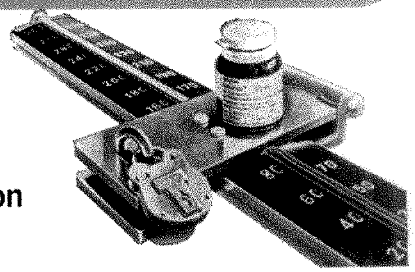

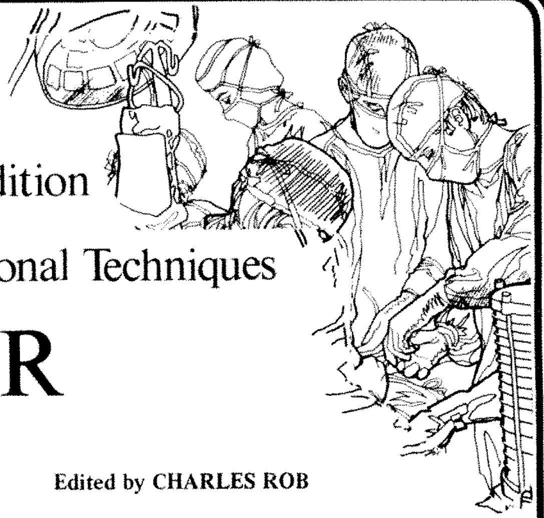

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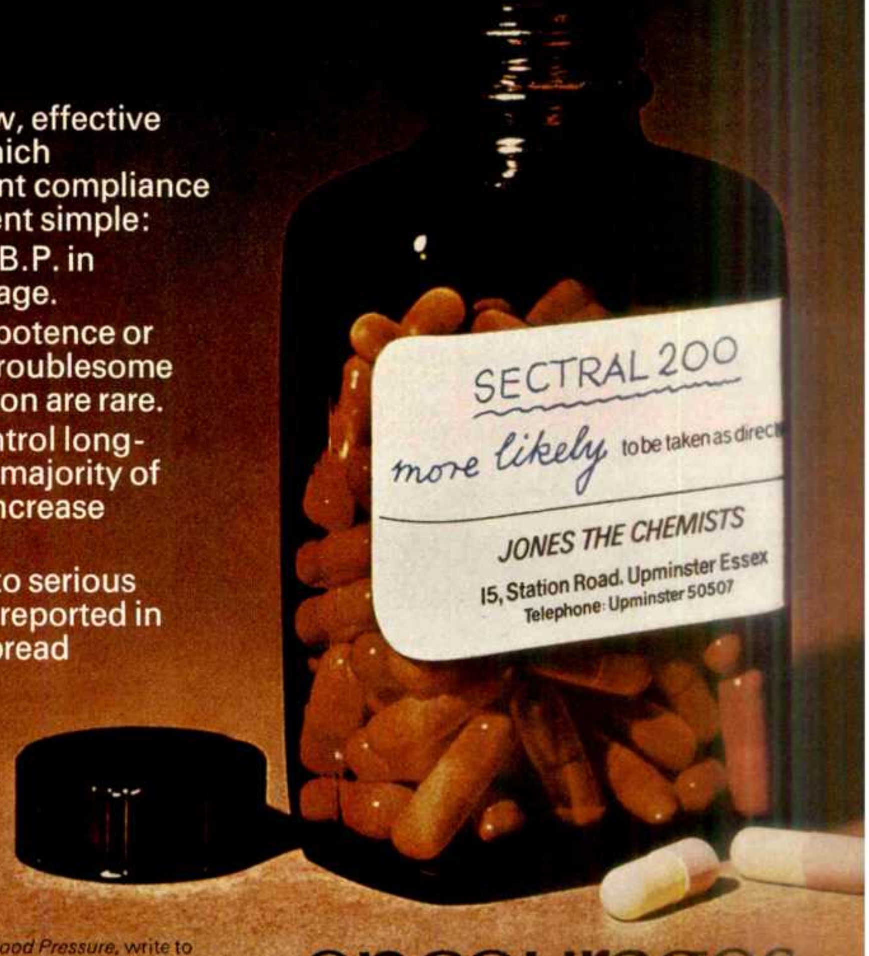

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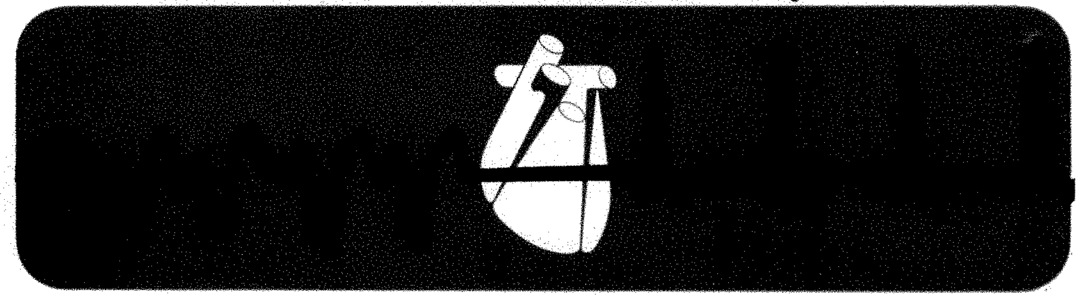

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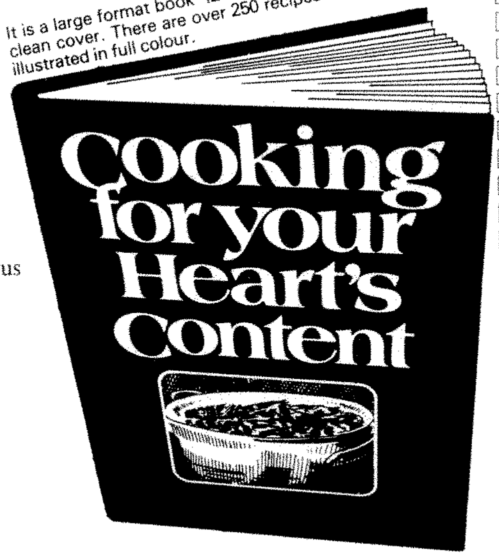

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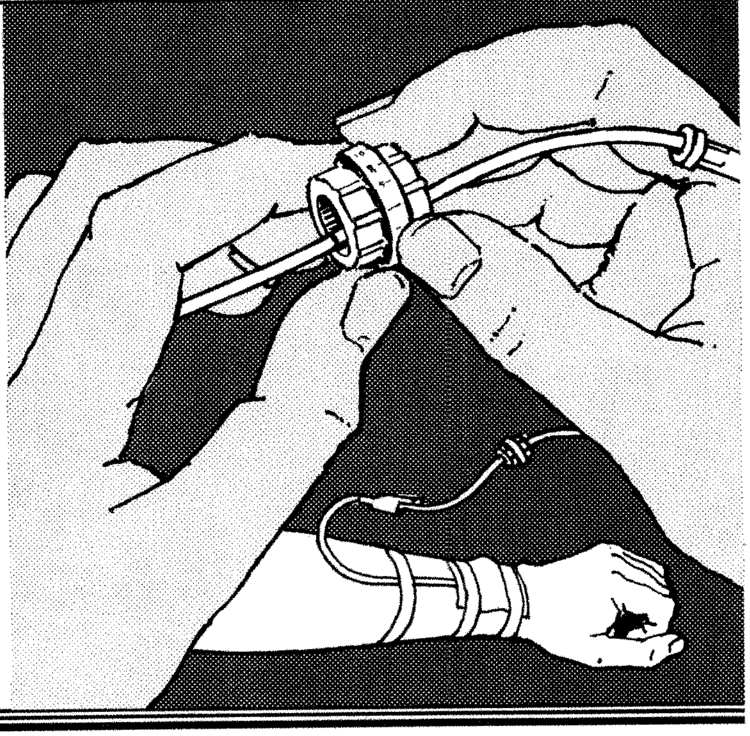

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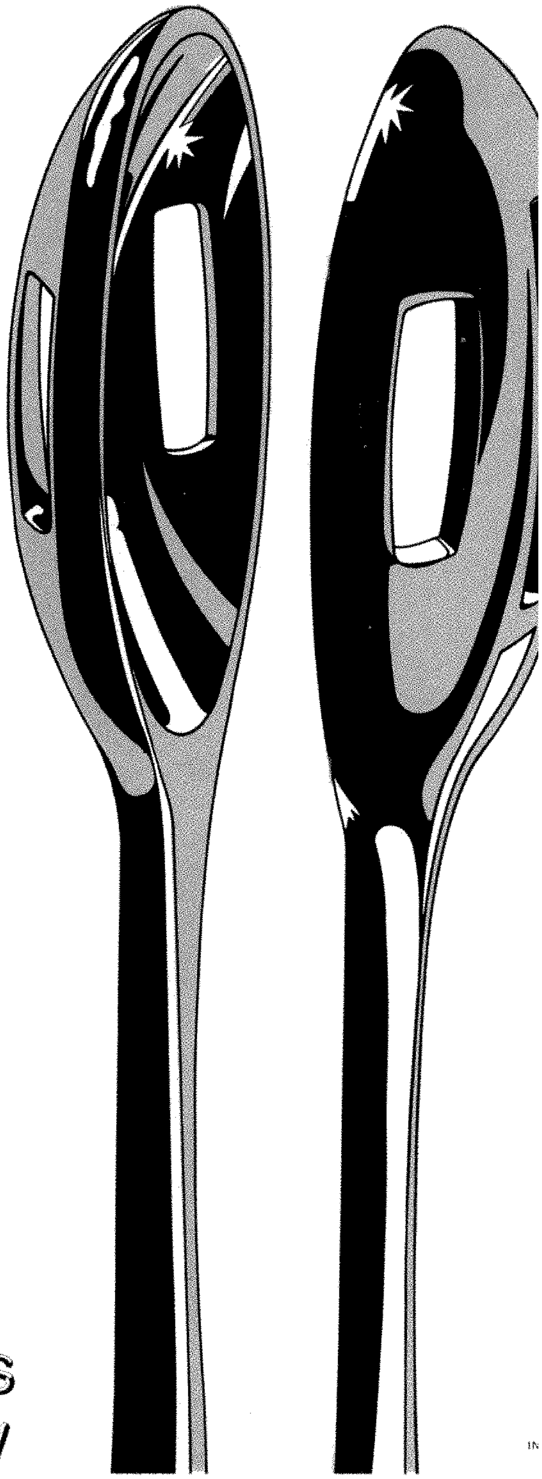

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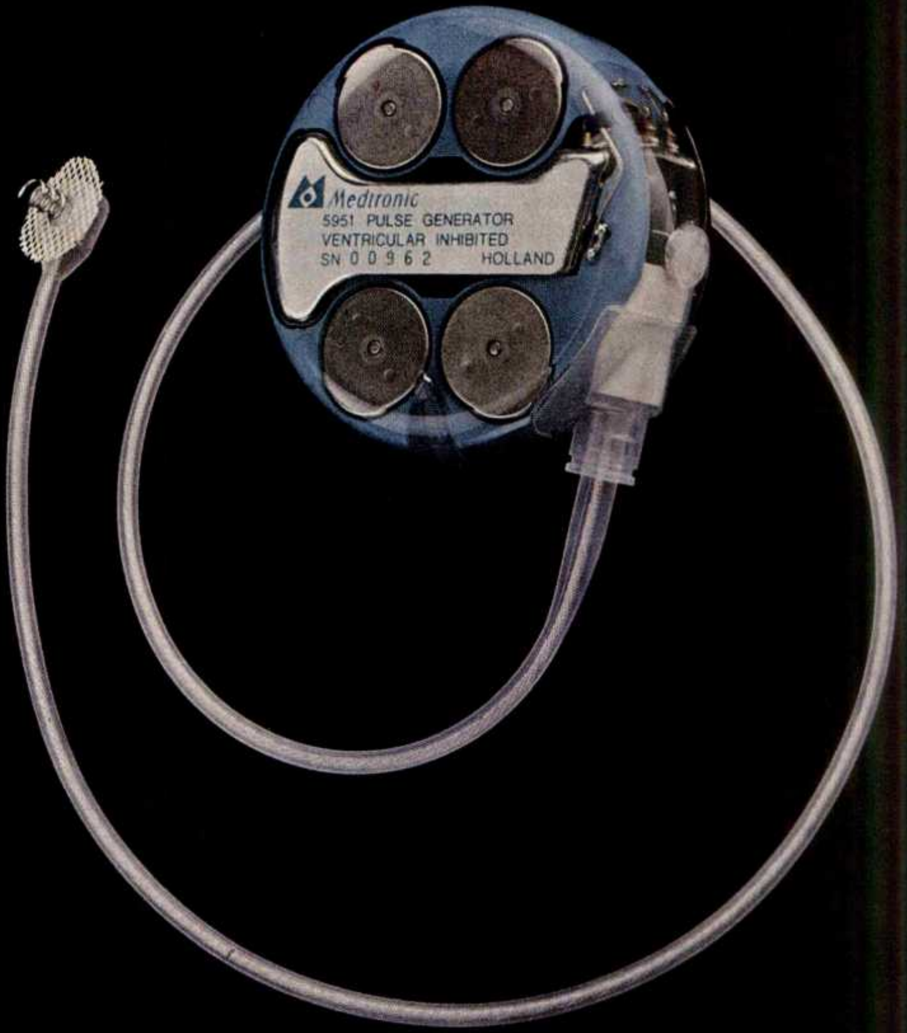

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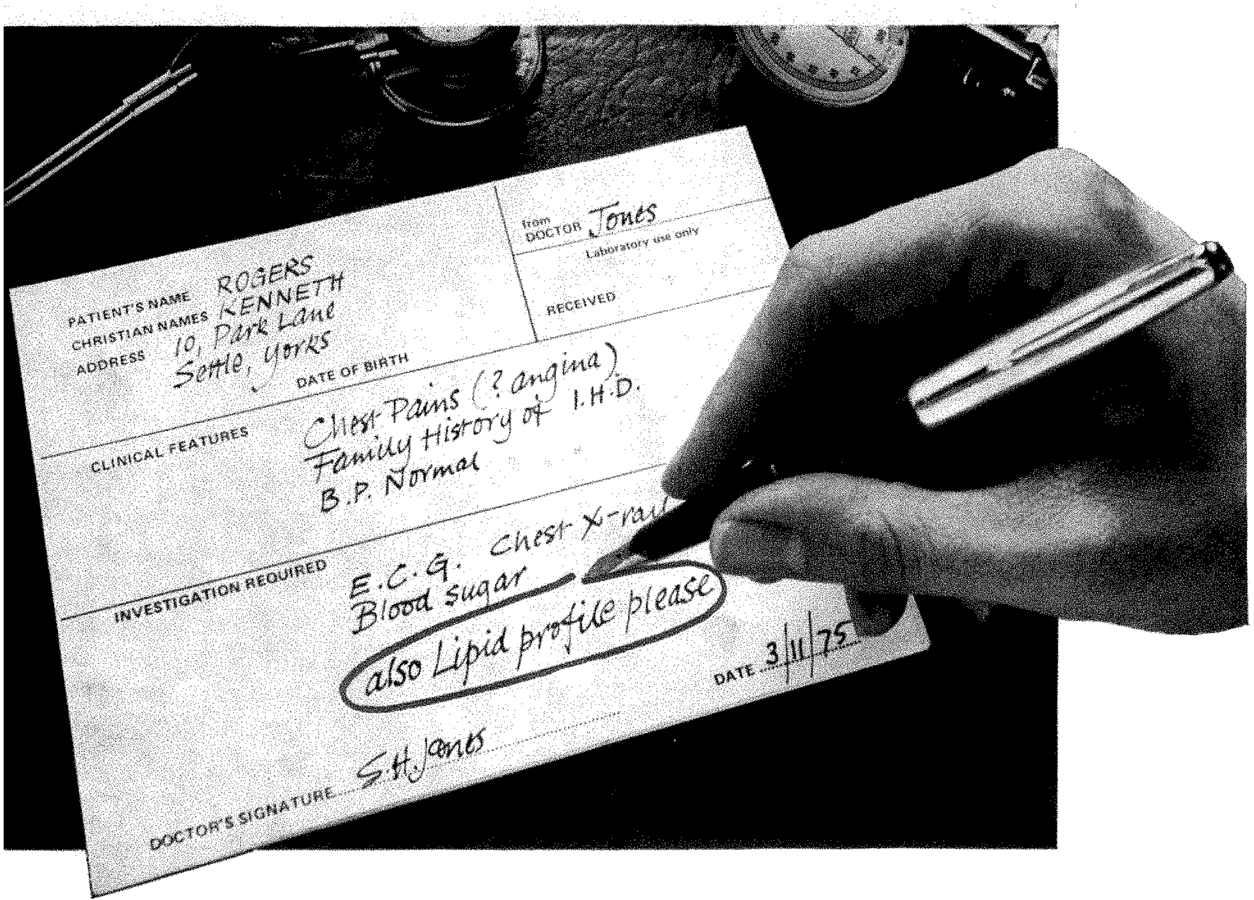

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PATIENT'S NAME ROGERS
CHRISTIAN NAMES KENNETH
ADDRESS 10, Park Lane
Settle, Yorks
DATE OF BIRTH

CLINICAL FEATURES Chest Pains (? angina)
Family History of I.H.D.
B.P. Normal

INVESTIGATION REQUIRED E.C.G. Chest X-ra
Blood sugar
also Lipid profile please

DATE 3/11/75

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1. Coronary Drug Project Research Group, 1975, *Journal of the American Medical Association* 231, 360.
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*British Heart Journal*, 1976, **38**, 1001–1009.

# Echocardiographic assessment of abnormal left ventricular relaxation in man[1]

M. T. Upton,[2] D. G. Gibson, and D. J. Brown
*From Brompton Hospital, London*

*In 64 patients requiring cardiac catheterization for chest pain, echocardiograms showing anterior mitral leaflet and left ventricular cavity simultaneously were recorded. These were digitized and their first derivatives computed in order to study time relations between mitral valve and left ventricular wall movement in early diastole. In 10 patients with normal left ventricular angiograms and coronary arteriograms, mitral valve opening began 1·1±9·3 ms (mean±SD) before the onset of outward wall movement, and reached peak opening velocity 2·0±13 ms after maximum rate of change of dimension. Virtually identical time relations were seen in 15 patients with normal left ventricular angiograms but with obstructive coronary artery disease (3·6±9·3 ms and 0·7±7·3 ms, respectively). These close relations were lost in patients with segmental abnormalities of contraction on left ventricular angiogram. In 19 such patients with normal septal motion, outward wall movement began 53±31 ms before the onset of anterior movement of the mitral valve leaflet, and this isovolumic wall movement accounted for 31 per cent of the total diastolic excursion. In 9 patients with reversed septal movement, these abnormalities were greater, 92±39 ms and 33 per cent, respectively, while in 11 patients with diffuse left ventricular involvement they were small, 5·5±13 ms and 3 per cent. Frame-by-frame digitization of cineangiograms was used to confirm these findings which appear to reflect an abnormal change in left ventricular cavity shape during isovolumic relaxation.*

Although systolic abnormalities of left ventricular contraction have been well documented in ischaemic heart disease (Herman and Gorlin, 1969; Baxley and Reeves, 1971), only recently have diastolic abnormalities of left ventricular relaxation been noted. Within the past 4 years, several angiographic studies have described the onset of outward wall movement occurring before mitral valve opening (Ruttley *et al.*, 1974; Altieri, Wilt, and Leighton, 1973; Hamby *et al.*, 1974; Wilson *et al.*, 1975), and the term segmental early relaxation phenomenon (SERP) has been used to describe this event. The diagnostic significance of these movements, however, is not clear since they were found whether or not ischaemic heart disease was present. The purpose of the present study was to see whether SERP could be detected by echocardiography in patients undergoing cardiac catheterization for the evaluation of chest pain, and to determine its relation, when present, to angiographic findings. In order to do this, echocardiograms of the anterior mitral valve leaflet and left ventricular cavity were recorded simultaneously at 100 mm/s, and a simple digitizing technique was used to compute instantaneous mitral valve velocity, left ventricular dimension, and its rate of change, so that the relation between mitral valve and wall movement in early diastole could be determined.

## Subjects and methods

### Subjects

Echocardiographic studies were performed on 64 patients who underwent cardiac catheterization for the evaluation of chest pain. Their ages ranged from 32 to 61, and 9 were women. All were in sinus rhythm and were studied within 24 hours of catheterization. They were selected only in so far as they were patients in whom it was possible to obtain acceptable echocardiographic records.

They were divided according to the findings at

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[1] Presented at 48th Scientific Sessions, American Heart Association, Anaheim, California, November 1975.

[2] Present address: Mary Hitchcock Memorial Hospital, Hanover, New Hampshire 03755, U.S.A.

catheterization into the following groups:

**Group 1** Ten patients with chest pain, but without occlusive coronary artery disease. Left ventricular haemodynamics and angiograms were also normal, and no cardiac cause could be found for their symptoms.

**Group 2** Fifteen patients with significant occlusive disease (greater than 70%) of one or more coronary artery, but with normal left ventricular haemodynamics and angiograms. None of these patients had electrocardiographic evidence of a previous transmural infarction.

**Group 3** Twenty-eight patients with significant occlusive coronary disease and segmental contraction abnormalities on angiogram; 20 of these had electrocardiographic evidence of a previous transmural myocardial infarction, and 14 had a raised left ventricular end-diastolic pressure (greater than 13 mmHg (1·7 kPa)). They were further divided according to septal movement at the time of echocardiographic study, into 2 subgroups: (3a) 19 with normal septal movement and (3b) 9 with reversed septal movement (anterior movement during systole).

**Group 4** Eleven patients with generalized impairment of left ventricular contraction and diminished ejection fraction (less than 30%). All had raised left ventricular end-diastolic pressure. Significant occlusive coronary artery disease was found in 4 of these patients who underwent coronary angiography, and a presumptive diagnosis of ischaemic cardiomyopathy was made in the rest from their histories.

## Echocardiographic methods

An Ekoline 20 ultrasonoscope (frequency 2·25 MHz; repetition frequency 1000/s) was used to make all measurements, and the output was displayed on a Cambridge multichannel photographic strip-recorder at a rate of 100 mm/s with a simultaneous electrocardiogram. The patients were studied in the left lateral oblique position with the transducer in the 3rd or 4th left intercostal space. The aortic root was first identified, and then the transducer was angled down through the mitral ring until echoes were obtained simultaneously from the anterior mitral valve leaflet, interventricular septum, and endocardium of the posterior wall (Fig. 1). Measurements were only made on those recordings showing clear, continuous echoes throughout a complete cardiac cycle. In addition, the posterior leaflet had to be recorded during at least part of diastole before the record was accepted. Wall movement was thus studied only at the level of the mitral valve.

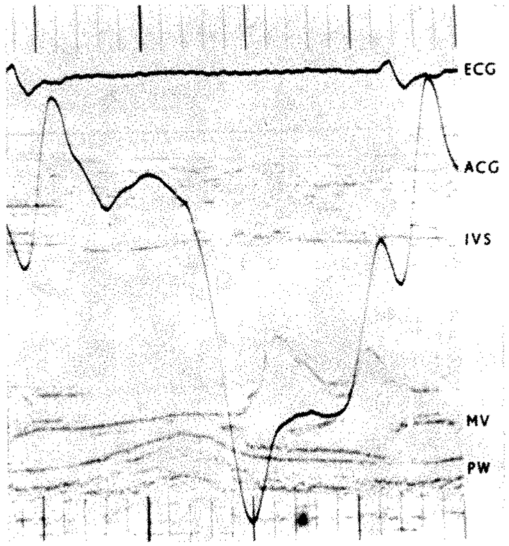

FIG. 1 *Echocardiogram of the left ventricular cavity from a patient with an abnormal left ventriculogram, showing interventricular septum (IVS), mitral valve cusps (MV), and posterior wall (PW). An apex cardiogram (AGG) is superimposed.*

## Angiographic methods

Left heart catheterization was performed retrogradely via the femoral artery. Immediately after left ventricular pressures were measured in the routine manner with a fluid-filled catheter, ventriculograms were obtained with the patient in the posteroanterior position. From 30 to 50 ml Triosil 75 per cent was injected into the left ventricle at a rate of 25 ml/s, and cine film was exposed at approximately 50 frames/s. An electrocardiogram was recorded throughout the injection and superimposed on the cine frames so that the film speed could be measured exactly. Calibration was carried out by means of a grid exposed at midchest level. Coronary arteriograms were performed using 3 to 8 ml injections of Urografin 76 by the Judkins technique and recorded in multiple views.

## Digitization

The method used to digitize the echocardiograms has been described elsewhere in detail (Gibson and Brown, 1973). The echoes of the septum, posterior wall, and anterior mitral leaflet were traced with a DMAC digitizing table interfaced with an IBM

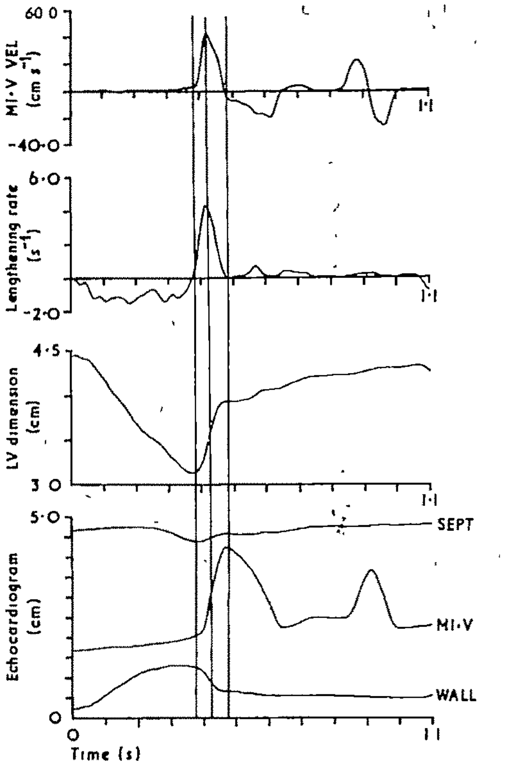

FIG. 2 *Digitized echocardiogram from a patient with a normal left ventriculogram. The lowest panel represents septal, mitral valve, and posterior wall echoes. Above are plotted left ventricular dimension (D), normalized lengthening rate (dD/dt/D), and anterior mitral valve cusp velocity. The three vertical lines correspond to the onset, peak, and discontinuity in outward wall movement.*

1800 computer. Strings of co-ordinates were generated for approximately 100 points on each of these echoes throughout a complete cardiac cycle, together with calibration signals representing 0·5 s, 1 cm, and the RR interval of the beat being studied.

Left ventriculograms of a representative number of patients from each group were also digitized in a similar manner (Gibson and Brown, 1975a). Ectopic and postectopic beats were excluded. Successive frames of the beat to be studied were projected on to the digitizing table, and the opacified ventricular cavity outlines were traced with the cursor. Strings of co-ordinates were generated for approximately 50 points on each frame, together with a reference point on the border of the cine frame.

## Analysis of data

The echocardiograms were analysed as previously described (Upton, Gibson, and Brown, 1976). From the stored digitized data, plots were made of the positions of wall and anterior mitral leaflet, instantaneous leaflet velocity, left ventricular dimension (D), and normalized rate of change of dimension (dD/dt/D) (Fig. 2). Peak velocities of leaflet movement during early diastolic opening (D-E) and mid-diastolic closure (E-F) were measured directly from the plots, as were the end-diastolic dimension and peak rate of wall movement during diastole. In addition, the time relation between wall and mitral leaflet movement in early diastole was analysed by measurement of the intervals between the time of (1) the onset of outward wall movement and that of mitral leaflet opening movement, (2) the peak rate of change of dimension and peak opening velocity of the leaflet, and (3) a discontinuity in the rate of wall movement previously

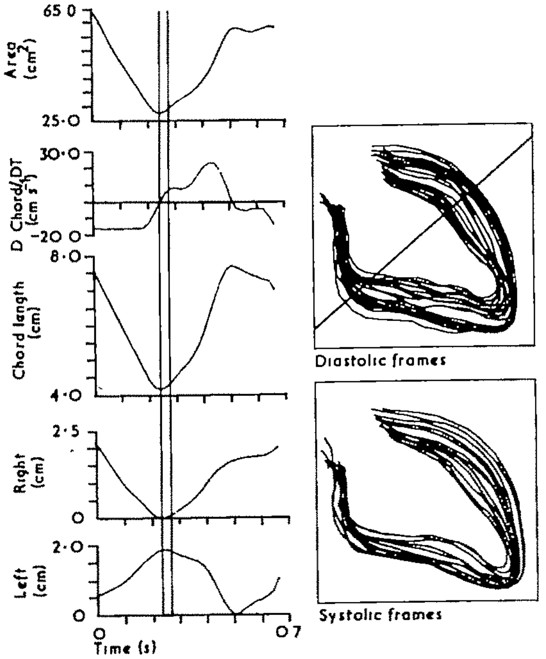

FIG. 3 *Digitized left ventriculogram, showing systolic (below) and diastolic (above) frames superimposed. The diagonal line represents the position of the chord studied. On the left are shown, from below, movement of the right and left sides of the cavity plotted against time, chord length and its rate of change, and cavity area. Vertical lines represent the timing of minimum cavity area and mitral valve opening.*

TABLE 1 *Echocardiographic data (mean values ±1 standard deviation)*

| | *Heart rate (beats/min)* | *Peak opening (D-E) velocity (mm/s)* | *Peak closing (E-F) velocity (mm/s)* | *Peak dD/dt/D* ($s^{-1}$) | *End-systolic dimension (cm)* |
|---|---|---|---|---|---|
| Chest pain with normal coronaries (10) | 67 ± 9 | 400 ± 60 | 240 ± 60 | 3·1 ± 0·48 | 3·2 ± 0·26 |
| IHD with normal LV angiograms (15) | 69 ± 7 | 360 ± 80 | 210 ± 50 | 2·9 ± 0·60 | 3·4 ± 0·38 |
| IHD with abnormal LV angiograms (19) | 73 ± 11 | 430 ± 90 | 210 ± 60 | 2·2 ± 0·63 | 4·1 ± 0·72 |
| IHD with abnormal LV angiograms and RSM (9) | 70 ± 8 | 420 ± 120 | 230 ± 70 | 1·7 ± 0·53* | 4·1 ± 0·67 |
| Cardiomyopathies (11) | 87 ± 14*** | 460 ± 70* | 210 ± 40 | 1·4 ± 0·40** | 6·3 ± 0·79*** |

*P<0·05 }
**P<0·01 } Statistical significance of difference from group with normal coronaries.
***P<0·001 }
IHD, ischaemic heart disease; LV, left ventricular; RSM, reversed septal movement.

TABLE 2 *Time interval from left ventricular wall to mitral valve movement (ms) (mean values ±1 standard deviation)*

| | *Onset* | *Peak* | *Discontinuity* |
|---|---|---|---|
| Chest pain with normal coronary arteries (10) | −1·1 ± 9·3 | 2·0 ± 13 | −1·3 ± 20 |
| IHD with normal LV angiograms (15) | 3·6 ± 9·3 | 0·7 ± 7·3 | −2·3 ± 16 |
| IHD with segmental contraction abnormalities on angiogram (19) | 53 ± 31** | 37 ± 28** | 33 ± 26** |
| IHD with segmental contraction abnormalities on angiogram and RSM on echocardiogram (9) | 92 ± 39** | 23 ± 23* | 35 ± 24** |
| Cardiomyopathies (11) | 5·5 ± 13 | 7·3 ± 18 | −3·3 ± 13 |

*P<0·01 }
**P<0·001 } Statistical significance of difference with respect to group with normal coronary arteries.

shown to coincide with the end of rapid filling (Prewitt *et al.*, 1975) and a corresponding discontinuity in the leaflet velocity tracing during mid-diastolic closure. In those patients in whom outward wall movement occurred before the onset of mitral leaflet opening movement, the increase in left ventricular dimension which occurred over this interval was measured and expressed as a percentage of total dimensional change during diastole. This technique also made it possible to delineate the different patterns of left ventricular wall movement which occurred during isovolumic relaxation.

The left ventriculograms and coronary angiograms were analysed and reported upon by two independent observers. In addition, in representative patients from each group, cavity outlines were plotted superimposed on one another from the stored data (Fig. 3). Those frames from the start of the beat being studied to the one with the smallest area were taken as systole and the remainder as diastole. Cavity area was derived by numerical integration and also plotted. In addition, a transverse diameter was drawn across the cavity outlines, displayed on a Ferranti MD4 visual display unit with the position of the cursor manually adjusted to represent the path of the ultrasound beam. Plots were thus made of the 'right' and 'left' sides of each chord analogous with the posterior wall and septal echoes, and left ventricular dimension and its rate of change were derived at this level. The time of mitral valve opening was determined by frame-by-frame analysis of the left ventriculograms and identified as the point when the first unopacified blood was seen in the left ventricle. The interval between the onset of outward wall movement and mitral valve opening and the percentage of total diastolic change in transverse dimension and cavity area during this interval could thus be assessed by a second method.

## Results

### Echocardiography (Tables 1 and 2)

**Group 1** In this group, with chest pain and normal coronary arteries, the heart rate was 67 ± 9, the peak lengthening rate was 3·1 ± 0·48 $s^{-1}$, and the end-systolic dimension was 3·2 ± 0·26 cm (Table 1). These values are similar to those previously reported for normal subjects (Gibson and Brown, 1973). The peak opening velocity was 400 ± 60 mm/s,

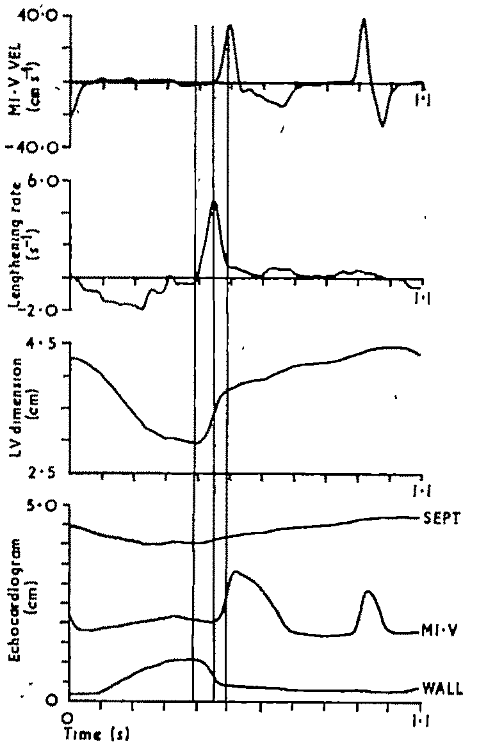

FIG. 4 *Digitized echocardiogram from a patient with an abnormal left ventriculogram. The layout is the same as in Fig. 2. The onset of mitral valve opening is delayed with respect to that of the increase of dimension, but coincides with its peak rate of change.*

and the peak mid-diastolic closure rate was 240 ± 60 mm/s. Again, these values agree with those previously reported in normal subjects (Upton *et al.*, 1976). In early diastole, there was a close time relation between left ventricular wall and mitral valve movement. The onset of mitral valve opening movement began 1·1 ±9·3 ms before the onset of outward wall movement (Table 2). The peak opening velocity of the valve followed the peak rate of wall movement by 2·0 ±13 ms, and later a discontinuity in the velocity tracing during mid-diastolic closure began 1·3 ±20 ms before a similar discontinuity in wall movement (Fig. 2). These corresponding events in mitral valve and wall movement occurred simultaneously, since the differences are not significantly different from zero. This close time relation has previously been noted in normal subjects (Upton *et al.*, 1976).

**Group 2** Using the same indices as above, this group with ischaemic heart disease and normal left ventriculograms could not be distinguished from group 1.

**Group 3a** These patients, with ischaemic heart disease and segmental contraction abnormalities on their left ventriculograms, could not be distinguished from group 1 with respect to heart rate, peak mitral valve opening and closing velocities, peak lengthening rate, and end-systolic dimension. The onset of mitral valve opening movement, however, began 53 ±31 ms after the onset of outward wall movement, and during this isovolumic interval, 31 per cent of total diastolic increase in transverse dimension occurred. The peak and discontinuity of the mitral valve velocity tracing were also delayed with respect to the corresponding events in wall movement with the time intervals being significantly increased compared with group 1 ($P < 0{\cdot}001$) (Fig. 4).

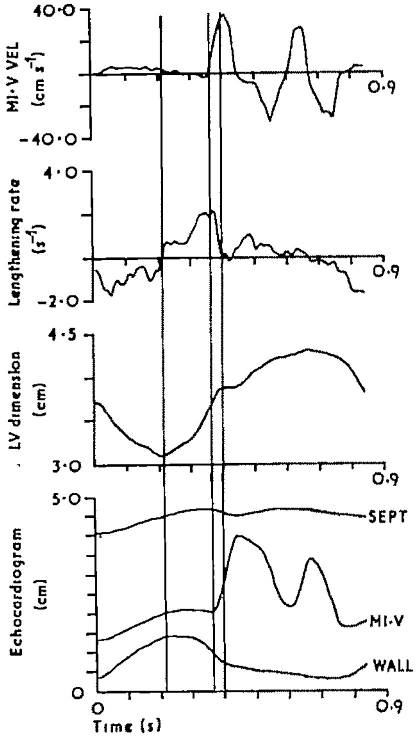

FIG. 5 *Digitized echocardiogram from a patient with an abnormal left ventricular angiogram. The layout is the same as for Fig. 2. Septal movement is reversed. The onset of mitral valve opening corresponds with peak rate of increase of dimension rather than with its onset.*

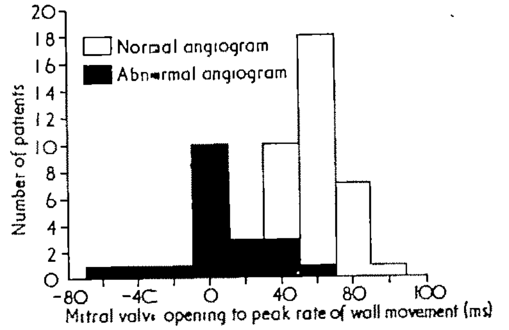

FIG. 6 *Distribution within the patient population of the time interval between the onset of mitral valve opening and the peak rate of increase in dimension in patients with normal and abnormal left ventriculograms.*

**Group 3b** In this group, with segmental contraction abnormalities on left ventriculogram and reversed septal movement on echocardiogram, mitral valve opening movement began 92 ±39 ms after the onset of outward wall movement, significantly longer than in group 3a (P < 0·01), with 33 per cent of total diastolic increase in transverse dimension occurring during this interval. Again, the peak and discontinuity of the mitral valve velocity tracing were also significantly delayed with respect to the corresponding events in wall movement. In addition, the peak lengthening rate of 1·7 ±0·53 $s^{-1}$ was significantly less than in group 1 (Fig. 5).

The relation between the onset of mitral valve opening and the peak rate of wall movement in patients with normal and abnormal left ventriculograms is shown in Fig. 6. In those with normal angiocardiograms, mitral valve opening occurred most frequently 50 ms before the time of peak rate of change of dimension; in the majority of patients with segmental abnormalities of contraction, the two events were simultaneous. The scatter about these mean values was similar in the two groups.

**Group 4** This group, with generalized impairn
of left ventricular contraction and decre
ejection fraction on angiogram (cardiomyopath
could easily be distinguished from group 1 with
usual criteria. The resting heart rate was si
ficantly higher at 87 ±14 beats/min (P < 0·0
the end-systolic dimension was raised significa
at 6·3 ±0·79 cm (P < 0·001), and the peak lengt
ing rate was reduced at 1·4 ±0·40 $s^{-1}$ (P < 0·
In this group, however, the onset of mitral v
opening was only 5·5 ±13 ms after onset of outw
wall movement, and only 3 per cent of the t
diastolic excursion occurred in this interval. Th
values were not significantly different from thos
group 1. In addition, the peak and the discontin
of the mitral valve velocity tracing correspon
closely to the corresponding peak and discontin
in wall movement, the time differences between
two not being significantly different from zer

## **Angiography** (Table 3)

**Group 1** In 5 representative patients from
group, the onset of mitral valve opening occu
85 ±13 ms after the onset of outward wall m
ment, and 21 per cent of the total increase in tr
verse dimension occurred in this time inte
This was associated with a 15 ±3·9 per cent incr
in cavity volume from the end-systolic v
(Fig. 3).

**Group 2** The results in 5 patients in this gr
studied angiographically were not significa
different from those in group 1.

**Group 3** In 10 representative patients from
group with segmental abnormalities shown by
ventriculography, mitral valve opening occu
140 ±36 ms after the onset of outward wall m
ment. Though 41 per cent of total diastolic m
ment along the transverse diameter occurred du
this interval, there was only a 12 per cent incr

TABLE 3 *Angiographic correlation with echocardiographic findings (mean ±1 standard deviation)*

| | *Time interval from onset of outward wall movement to MV opening (ms)* | *Per cent total wall movement before MV opening* | *Per cent total volume increase before MV opening* |
|---|---|---|---|
| Chest pain with normal coronary arteries (5) | 85 ±14 | 21 ±4 0 | 15 ±3 9 |
| IHD with normal LV angiograms (5) | 74 ±24 | 16 ±9·1 | 14 ±7 7 |
| IHD with segmental contraction abnormalities on LV angiogram (10) | 140 ±36** | 41 ±16** | 12 ±8·1 |
| Cardiomyopathies (5) | 65 ±22 | 17 ±6 3 | 11 ±8·5 |

**P < 0 001 Statistical significance of difference from group with normal coronaries.
MV, mitral valve.

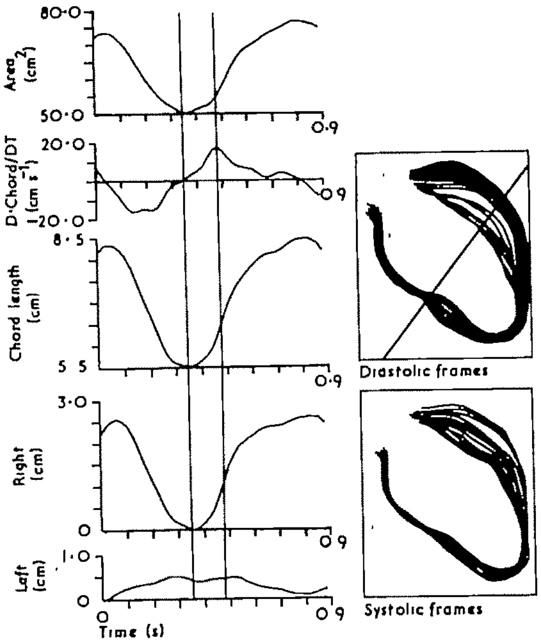

FIG. 7 *Digitized left ventricular angiogram from a patient with inferior hypokinesia. Layout as in Fig. 3. A significant increase in chord length has occurred before mitral valve opening.*

in area, the latter value not being significantly different from normal (Fig. 7).

**Group 4** Results in 5 patients in this group studied angiographically were not significantly different from those in group 1, with respect to the interval between the onset of outward wall movement and mitral valve opening and the percentage of transverse diameter and cavity area increase before mitral valve opening.

## Discussion

The present study has shown considerable variation in early diastolic events in patients presenting with anginal pain. In those with normal left ventriculograms, with or without coronary artery disease, the pattern of left ventricular wall movement was normal in early diastole, in that the onset and peak rates of outward wall movement were synchronous with those of anterior mitral valve cusp movement. In patients with angiographically demonstrable segmental abnormalities of contraction, however, the normal time relation between left ventricular wall movement and that of the mitral valve was disturbed. In almost all of them, outward left ventricular wall movement started before mitral valve opening, suggesting that it was occurring in the period of isovolumic relaxation, and thus was associated with a change in cavity shape rather than with filling. Isovolumic left ventricular shape changes have previously been studied angiographically, and have been described in normal subjects, and in patients with prolapsing mitral valve cusp (Gooch *et al.*, 1972) or ischaemic heart disease. They have previously not been detected by echocardiography, though an abnormality of systolic mitral motion described by Greenwald *et al.* (1975) may be explicable on the basis of mitral valve opening being late when compared with the onset of posterior movement of the mitral ring or posterior left ventricular wall.

In spite of its obvious limitations in depicting only regional function, echocardiography has certain advantages for studying left ventricular wall movement during early diastole. It enables the endocardium to be recognized unequivocally throughout this period of the cardiac cycle, when angiographic methods are open to question. It also allows mitral valve cusp movement to be observed and compared with that of the ventricular wall, and it avoids the introduction of a catheter into the left ventricle, so eliminating the possibility that early diastolic wall movement is caused by artefactual valvular regurtitation. Using echocardiography, it was possible to show that left ventricular wall movement was very abnormal in patients with segmental abnormalities of contraction shown by angiography. Instead of the normal synchronous movement of left ventricular wall and mitral valve cusp, there was a very significant increase in transverse dimension before the onset of ventricular filling. This resulted in the time of mitral valve opening being considerably delayed with respect to the time of minimum dimension. The commonest pattern of wall movement was of increasing rate of change of dimension, reaching a peak at the time of onset of forward movement of the anterior cusp. After this, the rate of increase of dimension dropped abruptly with a corresponding discontinuity on the dimension trace itself. Less commonly, the initial rate of outward movement was slow until the onset of forward movement of the anterior cusp but increased to normal values thereafter. This pattern merged into the normal one when the onset of mitral valve and wall movement were simultaneous. In 3 patients wall movement was very abnormal, with peak rates being registered before mitral valve opening, so that the rate of increase of dimension was already low at the start of filling, and declined still further until the succeeding left atrial systole. However, when considered together, all patients with segmental systolic abnormalities behaved as a single group, values for the interval between the onset of mitral valve and dimension change showing a normal frequency distribution about a value in which peak rate of change of dimension coincided with the onset of forward movement of the anterior cusp.

A surprising feature was the frequency with which these changes were detected by a method capable of studying only a small part of the ventricle. This suggests that the abnormality of early relaxation may be a generalized one, though related to a primary local disturbance of systolic function, possibly dependent on regional ischaemia. The direction and magnitude of the changes in dimension were unrelated to the localization of the systolic abnormality, but the relative delay in the onset of anterior movement of the mitral valve cusp was significantly greater when there was reversed septal movement. In contrast to patients with segmental abnormalities, these changes were not present when contraction was uniformly impaired because of severe ischaemic heart disease, stressing the importance of regional involvement in their genesis.

The relation between left ventricular dimension changes and mitral valve opening studied by angiography was significantly different in patients with normal left ventriculograms from that shown by echocardiography. Angiography showed that mitral valve opening was not synchronous but delayed with respect to the onset of outward wall movement, by a mean value of 85 ms, and during this period a mean increase of 21 per cent of the total diastolic excursion of dimension had occurred. The reason for this discrepancy is not clear, but it is likely to be the result of different methods of timing mitral valve opening. This was defined by echocardiography as the start of forward movement of the anterior cusp, and by angiography as the time of first appearance of unopacified blood within the left ventricular cavity. In some angiograms mitral valve movement itself was apparent as an early inward movement of the boundary of the cavity, followed by mid-diastolic closure, and in these records the frame in which unopacified blood was first considered to be present within the cavity coincided with peak opening rather than with the onset of forward movement (unpublished observations). This suggests that the angiographic definition of the onset of normal left ventricular filling identifies a point in time at least 50 ms later than that defined by the echocardiographic method. This result is compatible with that of animal studies (Pohost *et al.*, 1975) which have shown that the onset of forward movement of the anterior cusp precedes the start of left ventricular filling, taken as the time of crossover between left atrial and left ventricular pressures.

In patients with segmental contraction abnormalities, however, echocardiography was in agreement with angiography in showing a significant delay in mitral valve opening, both with respect to minimum dimension and cavity area, and during this period the increase in transverse dimension was significantly greater than that occurring in patients with normal left ventriculograms. This abnormality was present regardless of the site of the disturbance of contraction, being seen whether or not the dimension studied passed through the affected area. Related localized abnormalities have previously been described using angiography in patients with ischaemic heart disease, but these have been defined in terms of regional wall movement rather than as dimension changes as in the present study. During isovolumic relaxation, both inward and outward wall movement may occur in different parts of the cavity, the former being closely related to the pattern of coronary artery involvement, and the latter being, in part, compensatory. This reflects the fact that aortic and mitral valves are closed so that left ventricular volume cannot change. The resulting change in left ventricular cavity shape before mitral valve opening is always towards a more circular configuration in a single projection (Gibson, Prewitt, and Brown, 1976) and it is this that appears to be the basis of the dimension changes observed in the present study. An increase in minor diameter is a necessary consequence of cavity shape becoming more spherical, thus explaining how a regional disturbance anywhere in the ventricle can give rise to this single abnormality, detectable by echocardiography or angiography. Both methods show the frequent occurrence of increasing velocity of outward wall movement until mitral valve opening, suggesting that the isovolumic state is a necessary condition for the maintenance and propagation of this abnormality of wall movement, which resolves once ventricular filling begins. Patients with dilated left ventricular cavities and low ejection fraction show no significant shape change between systole and diastole (Gibson and Brown, 1975b) and so would not be expected to show any significant change in cavity configuration during isovolumic relaxation.

The present results clearly show that the echocardiographic dimension cannot be used to assess left ventricular filling in patients with systolic abnormalities of contraction resulting from ischaemic heart disease. This is particularly the case for estimates of peak rates of wall movement, which in the majority of cases, either preceded or were synchronous with the onset of mitral valve movement, and so could not possibly have been related to the rapid phase of ventricular filling. Similarly, the discontinuity on the dimension trace, which in normal subjects seems to indicate the end of rapid filling, in those with segmental abnormalities usually represented its start. It was not possible, either, to deduce the presence of these disturbances of left ventricular function from observations of the movement of the anterior cusp of the mitral valve during its opening or mid-diastolic closure. Whatever the mechanism of a reduced diastolic closure rate in left ventricular disease, it is not the result of segmental or generalized abnormalities of left ventricular contraction, a raised end-diastolic pressure, or incoordinate wall movement during filling. However, the results indicate that the versatility of the echocardiographic method can be increased in such patients by simultaneously recording echoes from the mitral valve as well as the left ventricular cavity and by using simple digitizing techniques. This allows isovolumic wall movements to be detected and distinguished from those caused by ventricular filling, and suggests that, when such disturbances are present, there is a high probability of the left ventricular angiogram showing segmental abnormalities of function.

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# Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease[1]

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*Left ventricular angiograms of 60 patients with ischaemic heart disease and 10 normal subjects were digitized frame by frame in order to study abnormalities of wall movement during the period of isovolumic relaxation. Plots were made of regional wall movement around the cavity throughout the cardiac cycle. In normal subjects 1·5 to 3·0 mm of symmetrical outward wall movement occurred during isovolumic relaxation, associated with an apparent increase of left ventricular volume of 10±4 per cent. The corresponding peak velocities of wall movement were 4·3 to 5·7 cm/s, significantly less than those recorded in the same region of the cavity after mitral valve opening. In patients with ischaemic heart disease, the following abnormalities were encountered:*

*(1) Abnormal inward movement, which, in single coronary artery disease, occurred in the area supplied by the affected vessel.*

*(2) Abnormal outward movement of more than 6 mm in non-affected areas which appeared to be a compensatory phenomenon.*

*(3) An abnormal cavity shape change towards a more circular configuration before mitral valve opening.*

*(4) Reduced peak rates of wall movement in affected areas during systole and filling.*

*It is concluded that such inward wall movement during isovolumic relaxation is abnormal and a sign of local ischaemia whose presence has significant effects on overall left ventricular function in both systole and diastole.*

Significant outward left ventricular wall movement has been shown to occur before mitral valve opening in normal subjects and in patients with prolapsing mitral valve cusp or ischaemic heart disease (Gooch *et al.,* 1972; Altieri, Wilt, and Leighton, 1973; Ruttley *et al.,* 1974; Hamby *et al.,* 1974; Wilson *et al.,* 1975). Such movements are usually reported as being localized to the antero-apical region though they may be accompanied by inward movement elsewhere around the left ventricular cavity border. However, there is still no general agreement as to their significance, since they have been considered a normal finding by some authors (Altieri *et al.,* 1973) and as a manifestation of asynchronous relaxation by others (Hamby *et al.,* 1974; Wilson *et al.,* 1975). Part of this uncertainty may arise from the technical difficulties in delineating a number of localized abnormalities occurring simultaneously around the border of the cavity and correlating them with measurements of overall ventricular functions such as changes in area or volume. This is particularly the case when angiograms are examined directly, frame-by-frame, and in order to reduce these difficulties, we have developed techniques for displaying information about local wall movement from single plane angiograms continuously throughout the cardiac cycle. Using these methods, it is possible to define abnormalities of left ventricular wall movement before mitral valve opening in greater detail than was previously possible, and to correlate them with overall ventricular function, and with the pattern of coronary artery involvement in patients with ischaemic heart disease.

## Subjects and methods

Studies were made on 70 patients who were under-

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going left ventriculography and coronary arteriography for the investigation of chest pain thought to be the result of ischaemic heart disease. Of these, 60 proved to have coronary artery disease, and the remainder had normal haemodynamics, left ventriculograms, and coronary angiograms. This latter group of patients is referred to as 'normal', though it is recognized that they all suffered from chest pain whose aetiology was undetermined and that minor or hitherto undescribed abnormalities of left ventricular function might have been present.

The patients were studied supine, and were premedicated one hour before the start of the procedure with 200 mg amylobarbitone sodium, given orally. Left ventriculography was performed in either the right anterior oblique or the posteroanterior position, and in 15 patients biplane posteroanterior and lateral films were obtained. Left ventriculography was always performed before coronary arteriography, using 35 to 40 ml Triosil injected at a rate of up to 25 ml/s. Cine film was exposed at 50 frames/s, and calibration was by means of a grid at midchest level. Multiple views of right and left coronary arteries were then obtained using Judkins' technique. Pressures were measured with a fluid-filled manometer system before the injection of any angiographic dye, and the zero level was the mid-thorax. Left ventricular end-diastolic pressure was taken as that before the start of the 'a' wave.

## Analysis of angiograms

Angiograms were analysed as previously described (Gibson and Brown, 1975a), frame-by-frame, using a Summagraphics digitizer and a Prime 300 computer system, and the information stored on disc for further calculations. Plots were made of superimposed cavity outlines during systole and diastole, a typical example being given in Fig. 1. Cavity area was calculated by numerical integration, and plotted throughout the cardiac cycle. Volume estimates were derived from area, and were used to calculate ejection fraction in the usual way. Left ventricular shape index was calculated as previously described (Gibson and Brown, 1975b) as $4\pi$ Area/Perimeter$^2$, which has a maximum value of 1 or 100 per cent when the cavity outline is circular, and which drops below this value when the outline is any other shape. Overall shape index changes throughout the cardiac cycle were noted, as well as those between the time of minimum area and mitral valve opening.

Plots of superimposed cavity outlines give only limited information about localized wall movement. In the angiogram illustrated in Fig. 1, it is apparent that the systolic frames show an area of inferior hypokinesia, but that the amplitude of wall movement in this area is normal during diastole. In addition, the diastolic frames also show a disturbance of wall movement involving the anterior

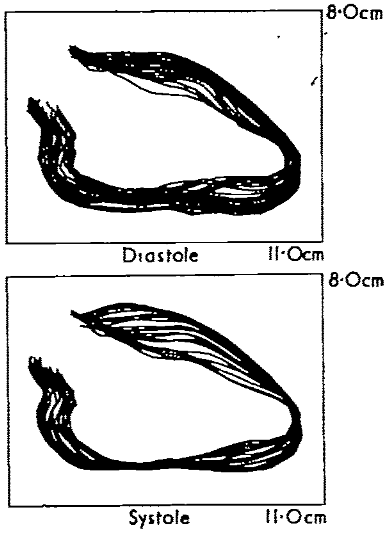

FIG. 1 *Successive cavity outlines from the left ventriculogram of a patient with right and circumflex coronary disease. There is inferior akinesia and an area of abnormal movement on the anterior margin during diastole.*

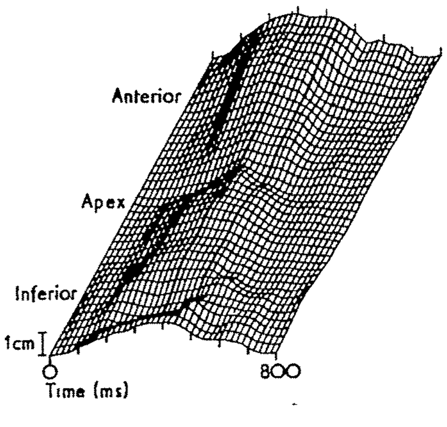

FIG. 2 *Plots of regional wall movement against time from a normal left ventriculogram. Each horizontal plot represents wall movement at one site around the perimeter of the cavity. The diagonal lines are isochrones, connecting events occurring simultaneously. The two accentuated isochrones represent the times of minimum area and mitral valve opening.*

wall, but give no information as to its direction or timing. A more comprehensive method of display is, therefore, required, which shows wall movement continuously throughout the cardiac cycle, in all regions of the cavity.

The method adopted was based on multiple plots of wall movement against time around the cavity. Forty equally spaced points were defined on the cavity outline of the end-diastolic frame, starting from the border of the aortic root, adjacent

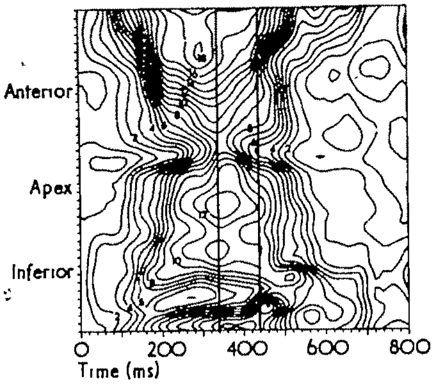

FIG. 3 *Display of inward wall movement with position around the cavity, and time from the same data as Fig. 2. Inward wall movement is indicated by contour lines, which represent distances in mm shown by the figures, from the position of the wall in the frame with maximum cavity area. The vertical lines represent the times of minimum cavity area and mitral valve opening.*

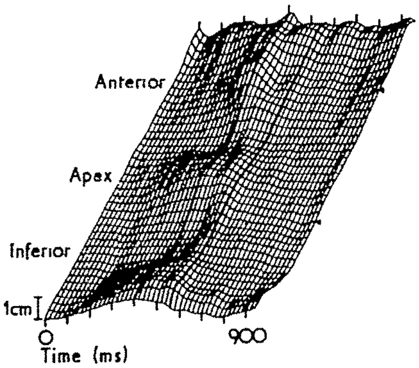

FIG. 4 *Plots of wall movement from the data of Fig. 1, with layout as in Fig. 2. During isovolumic relaxation, outward wall movement along the anterior border, and inward movement along the inferior surface are apparent. The two plots marked by arrows are analysed in more detail in Fig. 8.*

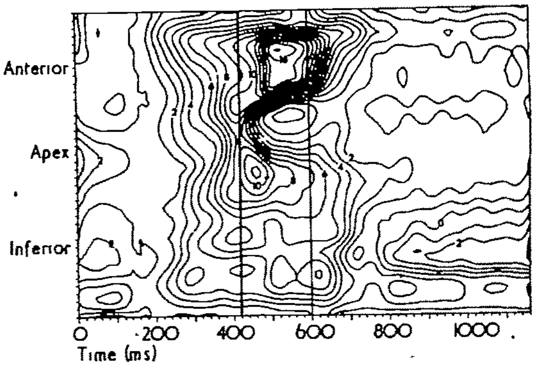

FIG. 5 *Display of wall movement in a patient with triple coronary artery disease. The layout is the same as in Fig. 3. Abnormal wall movement during isovolumic relaxation is apparent. For full description, see text.*

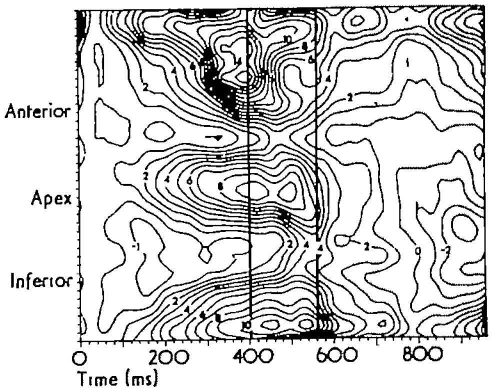

FIG. 6 *Display of wall movement from the same patient whose data are shown in Fig. 1. For description, see text.*

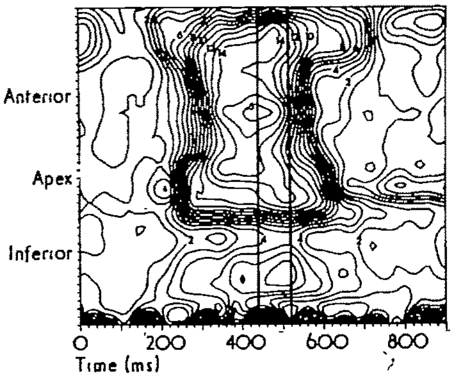

FIG. 7 *Display of regional wall movement from a patient with an inferior aneurysm. Wall movement elsewhere is normal. For full description, see text.*

to the mitral valve, and proceeding anticlockwise. From each, the nearest point on the end-systolic outline was sought, and along the line thus defined, wall position in each cine frame was measured and expressed in mm from the end-diastolic position. Local wall movement could have been displayed in a variety of ways, but it was noted that, if plots of movement against time for each line were stacked obliquely, with a series of isochrones superimposed, representing the timing of successive cine frames, then a three-dimensional impression was created, from which localized abnormalities of movement of the cavity outline could readily be discerned. Absolute values were derived from a 1 cm calibration bar plotted alongside all records (Fig. 2 and 4) and inward wall movement shown as an upward or positive deflection. This was a versatile method of display, but suffered from the disadvantage that systolic events appeared foreshortened in a view that gave optimal representation of diastolic events. Though this could have been remedied by adopting a negative deflection for inward wall movement, this led to foreshortening of diastolic events.

An alternative display, based on the same data, is shown in Fig. 3 and 5 to 7. Here, inward movement of the wall from its diastolic position in the frame with maximum cavity area, is indicated by contour lines, each joining points which have undergone the same displacement, and successive contours representing inward or outward movement of 1 mm.

Both types of display were interpreted in terms of events relating to the cavity as a whole. Isovolumic relaxation was taken as starting at the time of minimum cavity area and ending with mitral valve opening, which was identified as the timing of the frame in which unopacified blood from the left atrium first appeared within the left ventricular cavity. These two events were superimposed on all records.

### Analysis of records

Left ventricular wall movement during isovolumic relaxation was assessed from the displays of cavity outline constructed as described above. For simplicity, the cavity was considered in three regions: anterior, apical, and inferior. For each of these, the plot of its outline showing greatest inward or outward displacement was identified, and overall amplitude and direction of movement during isovolumic relaxation were noted. For these selected regions, plots were also made of velocity of inward or outward movement as in Fig. 8.

Left ventriculograms and coronary arteriograms were reported on by a radiologist who was unaware of the results of regional studies of wall movement.

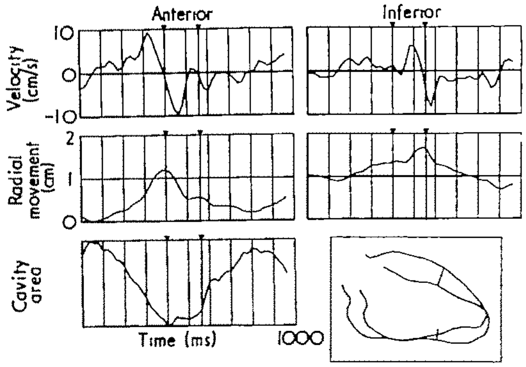

FIG. 8 *Plots of local wall movement and velocity against time, from anterior and inferior regions of the angiogram shown in Fig. 1. From below, panels represent change in cavity area, wall position, and rate of change of position with time. The origin of the two traces are shown diagrammatically in the panel on the right, and also in Fig. 4. The times of minimum cavity area and mitral valve opening are indicated.*

On the basis of this information, left ventricular contraction pattern was divided into one of the following groups: normal, segmental abnormality with normal ejection fraction (55% or greater), segmental abnormality with reduced ejection fraction, generalized impairment of function, and aneurysm, the last category being reserved for those patients in whom the diagnosis was confirmed at operation. Significant stenosis of a coronary artery was considered to be present if 70 per cent or more narrowing of the diameter of the lumen could be shown in any projection. No attempt was made to estimate collateral flow. The relation between abnormalities of wall movement during isovolumic relaxation and other manifestations of coronary artery disease was noted, including the pattern of coronary artery involvement, left ventricular contraction pattern, ejection fraction, and left ventricular end-diastolic pressure.

Standard t-tests were used to assess the significance of differences between means. 'Normal' values were taken as those lying within a range of 2 standard deviations of the corresponding means of the normal group.

## Critique of methods

### (1) Digitization procedure

This technique involves following the outer border of the image of the opacified left ventricular cavity with a cross-wire and identifying the co-ordinates of a relatively small number of points (about 100) on it. This procedure clearly contains a significant subjective element, particularly at end-systole when the cavity shape is irregular. In addition, it is not possible to follow minor irregularities of cavity outline using less than 100 points to define the cavity, so that an element of smoothing is introduced. However, as each outline is digitized separately, with no knowledge of the exact position of the previous one, reproducibility can be assessed from the relation of the border from frame to frame. Judged in these terms, it seems that the subjective component in the digitization procedure remains relatively constant throughout, but its absolute magnitude will only become apparent when comparison can be made with angiograms processed according to clearly defined algorithms.

### (2) Reference point for cavity outlines

There is, at present, no general agreement as to the way in which successive cavity outlines should be related to one another. It seems to be widely assumed that for each cine frame, a single point should be regarded as fixed, but it is not clear which point should be chosen. A number have been proposed, including the aortic root (Rees *et al.*, 1971; Helfant, Herman, and Gorlin, 1971), the intersection of major and minor axes (Hamilton, Murray, and Kennedy, 1972; Chatterjee *et al.*, 1973), a line from the apex towards the aortic root, dividing the cavity area into two halves (Leighton, Wilt, and Lewis, 1974), or an external reference (Chaitman, Bristow, and Rahimtoola, 1973). It must be stressed that all these solutions are merely approaches to the analysis of the angiographic image of the left ventricular cavity, and are all equivalent to one another, provided that relative movement of the reference points is known. None can give information additional to that in the angiogram itself.

### (3) Physical significance of cavity outline

The left ventricular cavity outline as displayed on an angiogram cannot be taken as representing the position of the corresponding region of left ventricular endocardium. Animal experiments have shown that the outer margin of the dye may be separated from metal markers on the myocardium itself, presumably by endothelial infolding, particularly at end-systole (Mitchell, Wildenthal, and Mullins, 1969). Outward movement of dye during early relaxation need not necessarily represent outward movement of endocardium, but could result from entry of dye-containing blood into the relaxing trabecular system. The irregular ventricular shape at end-systole may also result in the presence of concave, as well as convex, regions of wall, implying that the cavity boundary in a single projection need not necessarily represent continuous endocardium. In addition, if localized and rapid movements occur, different regions of wall may form the boundary at different times. The conclusion cannot be avoided that these factors represent definite limitations of the use of current angiographic techniques in studying wall movement at this time in the cardiac cycle.

### (4) Relation between wall movement and local function

A major objective of defining left ventricular wall movement is to use the information to assess local function. The solutions outlined above for expressing wall movement have been devised and validated in studies of systolic function, and it is not certain that an identical reference point should be used in diastole. Further, the present study is concerned with regional abnormalities of wall movement, and it cannot be assumed that, in these circumstances, a single reference point is valid for the whole cavity, or even for the same region at different times in the cardiac cycle. We have, therefore, taken the simplest method, referring cavity outlines to a fixed point on the margin of the cine frame (Chaitman *et al.*, 1973), and have attempted to define local movement in local terms by a method which allowed the direction in which it was measured to vary in different parts of the cavity in accordance with the orientation of the wall. Finally, we believe that the problem of the relation between wall movement and local function is a very complex one depending on such factors as ventricular architecture, local fibre orientation in different layers of the myocardium, and local constraints by other parts of the heart and extracardiac structures, and we do not feel that it can be solved by manipulation of reference points. As far as possible, therefore, other criteria have been used to corroborate conclusions about local ventricular function.

### (5) Use of single plane angiography

The use of single plane angiography has potential disadvantages in demonstrating regional abnormalities of movement, since only those near the perimeter in any projection are likely to be detected. In order to gain some idea of the sensitivity of the method in this situation, a comparison was made in 11 patients in whom posteroanterior and lateral angiograms were available, at least one of the pair showing an abnormality of isovolumic relaxation. The two planes agreed in estimating outward movement as either normal or abnormal in 9/11 cases, and inward movement in 5/11 cases. The results indicate the value of biplane angiography in studies such as the present one, and give some indication of the frequency with which abnormalities may be missed if only one projection is used.

## Results

### Normal subjects

In the 'normal' subjects, the mean interval between minimum cavity area and mitral valve opening was 93 ±13 ms (mean ±1 standard deviation) and, during this time, significant outward left ventricular wall movement occurred in all, leading to an apparent increase in volume equal to 10 ±4 per cent that at end-diastole. This was caused by 3·1 ±1·2 mm outward wall movement in the anterior part of the cavity, 1·7 ±2·0 mm at the apex, and 1·5 ± 2·5 mm along the inferior surface. In only 1 normal subject was inward movement observed in this period, of only 1 mm along the inferior surface. The peak velocity of outward wall movement during isovolumic relaxation was 5·7 ±2·7 cm/s along the anterior margin of the cavity compared with 12·5 ±2·8 cm/s after mitral valve opening. The corresponding figures for the apex were 4·6 ±4·5 and 9·0 ±3·0 cm/s, and for the inferior surface 4·3 ±3·4 and 9·3 ±2·8 cm/s. In all normals the velocity of outward wall movement was greater after mitral valve opening in all three sites. The overall pattern of left ventricular contraction and relaxation can best be appreciated from the display in Fig. 2 and 3, which indicate the synchronous onset of contraction, relaxation, and wall movement during filling common to all the normal group.

Mean ejection fraction in the normal group was 72 ±7 per cent, and the overall change in shape index in the cardiac cycle 28 ±7 per cent, of which 6 ±2 per cent occurred before mitral valve opening.

### Ischaemic heart disease

**Definition of abnormal wall movement** Although abnormal wall movement during isovolumic relaxation might have been defined in a number of ways, the most consistent appeared to be on the basis of the 95 per cent confidence limits for the amplitude of wall movement established in normal subjects during isovolumic relaxation. The amplitude of wall movement was thus considered to be increased if it was greater than 6 mm in an outward direction at any site around the cardiac border. Any inward movement along the anterior margin or inward movement with an amplitude of 2 mm or more at the apex or along the inferior border was also considered to lie outside the normal range.

**Frequency** The overall frequency of abnormal wall movement during isovolumic relaxation is given in Table 1, where its relation to the pattern of left ventricular contraction is shown. Increased amplitude of outward movement occurred in 25 patients, and most commonly involved the anterior margin of the cavity. Its commonest association was with segmental abnormalities of contraction in patients in whom ejection fraction was normal. Abnormal inward movement occurred in 42 patients, most frequently involving the inferior surface of the heart, and was even more closely associated with segmental contraction abnormalities, regardless of ejection fraction. Of these 42 patients, 17 showed outward movement elsewhere in the cavity, while of the 25 showing abnormal outward movement, inward

TABLE 1 *Relation of relaxation to contraction pattern*

| *LV contraction pattern* | *Abnormal outward movement* | | *Total* |
|---|---|---|---|
| | *Absent* | *Present* | |
| Normal | 8 | 8 | 16 |
| Segmental abnormality normal ejection fraction | 9 | 14 | 23 |
| Segmental abnormality low ejection fraction | 11 | 2 | 13 |
| Generalized impairment | 5 | 0 | 5 |
| Aneurysm | 2 | 1 | 3 |
| Total | 35 | 25 | 60 |
| | *Abnormal inward movement* | | |
| | *Absent* | *Present* | |
| Normal | 7 | 9 | 16 |
| Segmental abnormality normal ejection fraction | 4 | 19 | 23 |
| Segmental abnormality low ejection fraction | 1 | 12 | 13 |
| Generalized impairment | 4 | 1 | 5 |
| Aneurysm | 2 | 1 | 3 |
| Total | 18 | 42 | 60 |

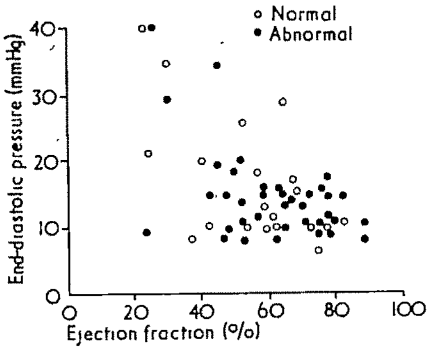

FIG. 9 *Relation of abnormalities of relaxation to left ventricular end-diastolic pressure and ejection fraction.*

movement was present elsewhere in all but 6. The relation between inward movement, ejection fraction, and end-diastolic pressure is shown in Fig. 9. In 12 patients only (20%) was the amplitude of wall movement normal during isovolumic relaxation.

**Site of abnormal movement** The relation between the pattern of coronary artery involvement and the site of abnormal movement is given in Tables 2 and 3. Isolated disease of the right coronary artery was associated with abnormal outward movement of the anterior surface, and isolated disease of the left anterior descending with that of the apex or inferior surface. When disease involved left anterior descending and right coronary artery or all three vessels abnormal outward movement was usually anterior, though any part of the cavity might be involved. The relation with coronary artery involvement was different for inward movement, in that isolated anterior descending disease was associated with inward movement along the anterior margin and isolated right coronary artery disease with abnormal inward movement along the inferior surface. With double or triple vessel disease inward movement was usually but not necessarily inferior.

TABLE 2 *Relation between site of abnormal inward movement and coronary artery involvement*

| *Site of abnormal inward movement* | *LAD* | *RCA* | *LAD RCA* | *Triple* |
|---|---|---|---|---|
| Anterior | 4* | 0 | 3 | 4 |
| Apex | 2 | 1 | 2 | 2 |
| Inferior | 0 | 5 | 9 | 10 |
| Total | 6 | 6 | 14 | 16 |

*1 patient with additional circumflex involvement.
LAD, left anterior descending; RCA, right coronary artery; Triple, 3-vessel disease.

TABLE 3 *Relation between site of abnormal outward movement and coronary artery involvement*

| *Site of abnormal outward movement* | *LAD* | *RCA* | *Cx* | *LAD RCA* | *Triple* |
|---|---|---|---|---|---|
| Anterior | 0 | 4† | 1 | 6 | 5 |
| Apex | 1 | 1 | 0 | 0 | 1 |
| Inferior | 4* | 0 | 0 | 2 | 0 |
| Total | 5 | 5 | 1 | 8 | 6 |

*1 patient with additional circumflex involvement.
†2 patients with additional circumflex involvement.

**Pattern of abnormal wall movement** The peak rate of wall movement during isovolumic relaxation was 10·3±3·0 cm/s in those regions showing abnormal *outward* movement, which was significantly greater than normal ($P < 0{\cdot}001$). In all but 5 patients, the velocity of outward movement during relaxation was greater than that during filling, the reverse of the normal pattern. In 8 patients peak velocity preceded mitral valve opening, while in the remainder (12) peak velocity of outward wall movement and mitral valve opening were synchronous. The mean velocity of outward wall movement during filling was 9·0±4·4 cm/s, significantly less than normal ($P < 0{\cdot}01$). The mean velocity of *inward* wall movement was 4·7±2·2 cm/s during isovolumic relaxation. The direction of wall movement reversed at the time of mitral valve opening, but during ventricular filling, the mean rate of outward movement was 6·8±4·0 cm/s, significantly less than normal ($P < 0{\cdot}001$). No regional differences in peak rates of inward or outward isovolumic wall movement were apparent.

**Systolic movement in affected areas** The peak rate of inward systolic movement was normal in those regions that showed abnormal outward movement during isovolumic relaxation. However, regions showing inward movement during isovolumic relaxation showed a reduced rate of movement during systole. Very similar values were observed whether the anterior part of the ventricle was involved (peak systolic inward velocity 4·3±1·9 cm/s) or the inferior region (3·2±1·6 cm/s). These were significantly less than normal ($P < 0{\cdot}001$) and also less than unaffected regions of the same ventricle ($P < 0{\cdot}001$).

Examples of disturbances of left ventricular wall movement occurring in patients with ischaemic heart disease are shown in Fig. 5 to 7. In the patient whose angiogram is represented in Fig. 5, the onset of inward wall movement is synchronous, though its velocity is reduced. During isovolumic relaxation, however, there is striking inward movement of the anterior border and outward movement of the apex, which has reached its diastolic position at the time of mitral valve opening. A more complex disturbance is illustrated in Fig. 6. The onset of inward wall movement is asynchronous, being delayed in the inferior part of the cavity, where amplitude and velocity of wall movement are also reduced. Inward wall movement involving the apex and inferior surface and outward movement anteriorly occur during isovolumic relaxation, and, finally, the velocity of wall movement during ventricular filling is reduced in all parts of the cavity. By contrast, the patient illustrated in Fig. 7 has an inferior aneurysm. Though the amplitude of wall movement is greatly reduced in this region, it is normal elsewhere throughout the cardiac cycle.

**Overall left ventricular function** The presence of abnormal wall movement during isovolumic relaxation appeared to have significant effects on overall left ventricular function. The interval between the time of minimum area and mitral valve opening was increased in all patients with ischaemic heart disease, to a value of 120 ±18 ms when no isovolumic wall movement was apparent, and to 150 ±30 ms when abnormalities were present. These changes are significantly different from one another ($P < 0{\cdot}001$), and also from normal ($P < 0{\cdot}001$). Overall changes in left ventricular cavity shape were also abnormal in patients with ischaemic heart disease. The total reduction in shape index during systole was 16 ±3 per cent in those patients with impaired isovolumic relaxation and 15 ±10 per cent in those without, values not significantly different from one another. In order to allow comparison with the normal group, values were calculated for patients with ischaemic heart disease and normal ejection fraction. The corresponding figures were 18 ±6 per cent for patients with abnormal relaxation and 16 ±6 per cent for those without, both values being significantly less than normal ($P < 0{\cdot}001$). However, when the change in cavity shape index occurring in the interval between minimum area and mitral valve opening is considered, patients with ischaemic heart disease and normal wall movement during this period showed a normal increase of 4 ±2 per cent, while in patients with abnormal wall movement, but normal ejection fraction, it was 9 ±5 per cent, or half the total change occurring in the cardiac cycle. The latter value was significantly greater than normal, expressed in absolute terms and also as a proportion of the total change in shape index occurring in the cardiac cycle ($P < 0{\cdot}001$).

## Discussion

Isovolumic relaxation of the normal left ventricle is a complex process. Angiographic studies have shown that outward wall movement occurs while mitral and aortic valves are both closed, so that left ventricular cavity volume increases. There is no generally agreed explanation for this, though several mechanisms have been proposed, including herniation of the mitral valve apparatus or downward movement of the aortic valve cusps and the blood contained between them (Ruttley *et al.*, 1974) into the left ventricle. In spite of the increase in cavity size, the period between the end of ejection and mitral valve opening is usually referred to as that of isovolumic relaxation, a convention we propose to follow.

Our results confirm previous ones in showing this outward wall movement (Altieri *et al.*, 1973; Ruttley *et al.*, 1974), though the method of display used enabled variation in its localization and extent to be more easily appreciated. The time of maximum inward movement at the end of systole was almost synchronous throughout the ventricle, and thus occurred simultaneously with minimum area. Outward wall movement before mitral valve opening was shown in all normal subjects, with no significant variation in its amplitude in different parts of the cavity. Inward movement occurred in only one subject, where it was confined to the inferior surface and its extent was small. The corresponding peak rates of wall movement were low and uniform in all regions of the ventricle. Cavity size increased slowly at first, but as the mitral valve opened, there was a sudden increase in its rate of change. This was reflected in local rates of outward wall movement which abruptly and uniformly increased, with significantly greater rates being recorded along the anterior margin than elsewhere. Isovolumic wall movement caused a significant change in cavity shape which became more circular. This was expressed quantitatively as a small increase in shape index of 6 per cent before mitral valve opening, compared with that of 22 per cent occurring during filling.

In the presence of ischaemic heart disease, this ordered process was frequently disturbed by two abnormalities of isovolumic relaxation occurring with approximately equal frequency: (1) excessive outward movement and (2) inward wall movement, the former being commoner along the anterior and the latter along the inferior margin of the cavity. Both types were often to be seen in the same cavity, and were probably complementary since, with mitral and aortic valves shut, excessive outward movement in one part of the cavity could only have been possible with inward movement elsewhere. In many patients, detection of only one abnormality was probably a limitation of single plane angiography, though when ejection fraction was low, failure to document outward wall movement as excessive reflected the use of criteria derived from normal subjects in patients in whom the amplitude of wall movement was reduced. These disturbances were frequently associated with segmental contraction abnormalities, and their distribution within the ventricle was characteristic in that the region of inward movement corresponded to that supplied by the involved coronary artery in patients with single vessel disease. In addition, these same regions showed delayed onset and significantly lower rates of inward movement during systole in comparison with other parts of the ventricle. We conclude that this pattern is the primary abnormality during isovolumic relaxation, and represents the behaviour of myocardium supplied by diseased coronary arteries. Conversely, excessive outward movement was confined to regions with normal systolic function and a normal coronary supply in patients with single vessel disease, strongly suggesting that it was a secondary phenomenon, a conclusion consistent with previous studies (Ruttley *et al.,* 1974). The overall result of both was for left ventricular cavity shape to become significantly more circular before mitral valve opening, though the shape change during filling was significantly less.

Angiography was used in the present study to depict abnormalities of wall movement because it appeared to be the only one available to us capable of demonstrating rapid motion in different parts of the cavity. However, it has serious drawbacks, as has been pointed out. The first of these is the uncertain relation between the outer border of dye and the endocardium, particularly at end-systole. The same events were therefore studied by M-mode echocardiography, using a different physical principle to detect endocardium and record its motion throughout the cardiac cycle along with that of the anterior cusp of the mitral valve. The ability of this method to record related dimensional changes before mitral valve opening provides confirmatory evidence for their presence (Upton, Gibson, and Brown, 1976). A second problem inherent in any study which attempts to deduce regional abnormalities of function from wall motion is the extent to which the events described are local phenomena and the extent to which they result from overall movement of the heart within the thorax. The reasons for selecting the methods used in the present study have been discussed above, but it is possible, for example, that the apparent asymmetry of wall movement in normal subjects after mitral valve opening, with accentuation of that of the anterior wall, can be regarded as equivalent to slight overall movement of the heart upwards and to the left. By contrast, abnormal wall movements in patients with ischaemic heart disease appear to be truly local events, not only from their predictable relation to the pattern of coronary artery involvement, but also in view of the significantly greater velocities and consequently greater accelerations involved. If these local velocities are to be explained in terms of movement of the heart as a whole, the presence of large forces to produce the observed accelerations is implied, for which there is neither experimental evidence nor explanation.

Although it was not specifically designed to give information about basic mechanisms, the present study allows deductions to be made about the disturbances of function underlying the abnormalities of movement here described. Asymmetrical wall movement appears to be caused by regional ischaemia. It is closely associated with depressed systolic function, occurs in the territory supplied by diseased coronary arteries, and has been reported to regress after successful saphenous bypass grafting (Hamby *et al.,* 1974). Depressed systolic function itself was not the primary cause since, in some patients, it occurred in the absence of any abnormality of relaxation (Fig. 7) while in others, maximum isovolumic inward wall movement was present in regions adjacent to those showing maximum depression of systolic function (Fig. 4). These abnormally relaxing areas seem to have reduced, but not absent systolic function, and so may represent transitional zones between normal and irreversibly damaged myocardium. Delayed relaxation of such an area would lead to tension persisting longer than elsewhere, and so to inward movement during early relaxation. Other possible explanations include myocardial distortion resulting from persistence of shear forces developed during systole or the direct effect of abnormal cavity shape at end-systole, since differences in regional tension depend on local curvature. Whatever the mechanism, it seems that observation of left ventricular wall movement during isovolumic relaxation can be used to give information about the physiological properties of the myocardium to supplement that obtained from recording systolic events.

Abnormalities of isovolumic relaxation may impair overall left ventricular function for a number of reasons. Outward wall movement, when ventricular pressure is still raised, is associated with loss of efficiency in energy transfer from myocardium to the circulation and, therefore, in depressed systolic function (Gibson and Brown, 1976). Prolongation of the period of relaxation, associated with a reduced peak rate of fall of ventricular pressure (McLaurin, Rolett, and Grossman, 1973) and delayed mitral valve opening, will impair filling at high heart rates, even if no other disturbance is present, simply by reducing the time available for inflow of blood. In addition, abnormal wall movement during isovolumic relaxation was associated with a reduced rate of outward movement after mitral valve opening and, therefore, with an abnormal filling pattern. We have previously suggested that part of the increase of ventricular volume during the rapid phase of filling may be accommodated by the cavity becoming more spherical (Gibson and Brown, 1975b). A change in cavity shape before mitral valve opening, and a reduced shape change during filling would interfere with this mechanism causing a reduction in ventricular compliance calculated from the ratio of pressure and volume changes without any alteration in the passive elastic stiffness of the myocardium itself. This effect may contribute to changes in compliance observed during angina or after trinitrin administration (Barry *et al.*, 1974).

These fundamental disturbances caused by abnormalities of isovolumic relaxation in patients with ischaemic heart disease stress the remarkable nature of this process in normal man. It seems that an investigation of the events of early diastole can usefully be undertaken in any patient in whom overall left ventricular function appears to be impaired.

The computing equipment used in these studies was provided by the DHSS as part of their experimental computer programme.

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# Acute myocardial infarction
## *Evaluation of praecordial ST segment mapping*[1]

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*In 38 patients with acute anterior myocardial infarction or ischaemia, the extent and amplitude of ST segment elevation was measured on the chest wall with a praecordial mapping technique. There was a poor correlation with measurements of clinical severity and with the extent of necrosis as measured by the peak levels of creatine kinase (CK) and the estimated total amount of CK released. In two patients ST segment re-elevation occurred without re-elevation of serum CK and in two other patients reinfarction obvious on enzyme re-elevation occurred without changes in ST segments. Praecordial ST segment mapping appears to have a limited role in measuring or monitoring human infarct size and would be an unreliable tool for evaluation of methods to limit myocardial necrosis. The chest leads of the standard 12-lead electrocardiogram provided sufficient information for clinical evaluation of ST segment elevation.*

It has been shown that the extent of myocardial necrosis after experimental coronary occlusion can be limited by appropriate interventions (Maroko *et al.*, 1971; Braunwald and Maroko, 1974). Clinical application of these findings is possible only if accurate methods of measuring and following trends in infarct size in patients can be developed. Mapping of the ST segments of the electrocardiogram in the praecordium has been proposed (Maroko *et al.*, 1972; Reid *et al.*, 1974) for this purpose. Despite adequate documentation of the validity of ST segment elevation as an index of infarct size in dogs (Maroko *et al.*, 1971), it is not known how accurately ST segment changes in the praecordial electrocardiogram reflect changes in human myocardial infarction. Theoretical considerations (Boineau, 1971) and preliminary clinical reports (Reese, Scheidt, and Killip, 1973) suggest that use of the technique in measuring human infarct size requires critical evaluation.

The present study was undertaken to evaluate the technique and compare it with clinical and enzymatic estimates of infarct size.

## Patients and methods

Studies were made on 38 patients with suspected acute anterior or anterolateral myocardial infarction. Altogether 313 praecordial ST segment maps were recorded. The diagnosis was based on the clinical features and the results of routine daily serum enzymes and electrocardiograms. On WHO Criteria (World Health Organization, 1969) there were 35 patients with 'definite' and 3 patients with 'possible' myocardial infarction. In 17 patients praecordial maps were performed soon after admission to hospital, each morning for 10 consecutive days, and on the day of discharge from hospital. The day of admission to hospital is referred to as day 1.

### Technique of praecordial ST segment mapping

All recordings were made with the patient in the supine position. The chest wall of male patients was shaved. Forty-two positions were marked on the anterior chest wall; indelible felt pencil was used and markings were retouched daily to ensure accurate placement of the recording electrode. A Philips class B electrocardiograph was used. The amplitude frequency response (without muscle filter) was linear from 0·3–150 ± 10 per cent Hz with maximum 10 per cent at 150 Hz, time constant 2 seconds. All recordings were done on standard electrocardiograph paper running at 25 mm/s with standardization of 1 cm/mV. Approximately 15 minutes were required for recording each 42 lead electrocardiogram.

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The maximum height of the ST segment was measured to the nearest 0·5 mm from the isoelectric line (TP segment). When the ST segment was upward sloping the maximum height was taken at a point immediately preceding the origin of the T wave (determined in a lead where the T wave was clearly demarcated). This point varied from 0·6 to 0·12 s from the R wave. The recordings and measurements were made throughout by the same observer (VK). The amplitude of the ST segments measured in each recording position were summed and expressed as the sum ST (ΣST). The number of cells showing ST segment elevation of >0·5 mm was expressed as NST and an ST segment map was constructed. On patients who had consecutive daily recordings the mean of the ΣST ($\overline{\Sigma ST}$) and the mean of the NST ($\overline{NST}$) was calculated by dividing by the number of days on which recordings were made. For comparison with 12 lead tracings, standard electrocardiograph records were taken on the same machine and ST segment measurements performed by the same observer.

### Serum enzyme estimations

Creatine kinase was estimated (a) each morning for 5 to 6 days and (b) every 2 hours from admission until the serum enzyme levels returned towards normal. Blood samples were taken from an indwelling catheter in a central vein, stored at 4°C, and separated within several hours of sampling. The enzyme was measured by a standard autoanalyser technique (Siegel and Cohen, 1967).

### Estimation of cumulated CK release

From the results of the 2-hourly CK estimations, the total amount of CK released was calculated by a modification of the formula of Shell, Kjekshus, and Sobel (1971). This technique has been previously shown in experimental animals to reflect the total amount of CK released into the serum.

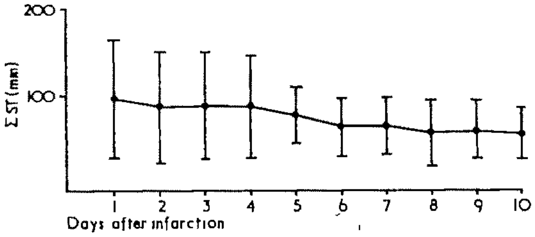

FIG. 1 *ST on days 1 to 10 of hospital course. Mean ± SD, n=17.*

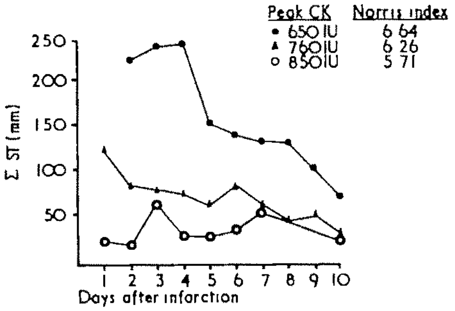

FIG. 2 *ST in 3 patients of approximately equivalent enzyme rise (peak CK) and clinical severity (Norris index). Note the differences in patterns of ST segment elevation in 3 patients.*

### Clinical data recording

Each patient had past history, admission physical examination, electrocardiogram, and chest *x*-ray tabulated on admission; haemodynamic complications and arrhythmias were recorded daily. Clinical severity was calculated by the methods of Peel *et al.* (1962) and Norris *et al.* (1969). Survivors were reviewed at 6 weeks to assess physical capacity (NYHA classification).

## Results

The ΣST on day 1 was 102±63·5 mm and progressively declined to 62±27·4 mm by day 10 (Fig. 1). There was a wide variation between patients: the ΣST on day 1 ranged from 23·5 to 280·5 mm. The standard deviations from the mean ΣST was >50 per cent for each of days 1 to 10. The trends in ΣST varied, even for patients with approximately similar clinical and serum enzyme abnormalities (Fig. 2). Similar trends were observed in NST.

### Comparison with clinical estimates of severity

The ΣST on day 1 or the $\overline{\Sigma ST}$ did not correlate with clinical grades of severity of infarction as

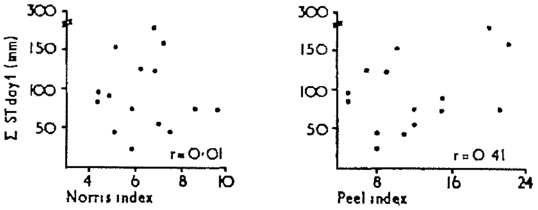

FIG. 3 *Correlation between ST on day 1 with clinical indices of severity of infarction.*

TABLE 1 *Comparison of ΣST day 1 and $\Sigma\overline{ST}$ with various subgroups: there were no significant differences in ST segment elevation between any subgroups*

| | | *ΣST day 1* | | *$\Sigma\overline{ST}$* | |
|---|---|---|---|---|---|
| | | *n* | *Mean ±SD* | *n* | *Mean ±SD* |
| Age >60 | | 6 | 66±54 | 7 | 82±43 |
| <60 | | 9 | 117±64 | 10 | 97±40 |
| Previous infarction | Yes | 5 | 79±42 | 6 | 86±41 |
| | No | 10 | 135±79 | 11 | 86±43 |
| Previous angina | Yes | 5 | 87±43 | 6 | 69±27 |
| | No | 10 | 107±74 | 11 | 102±45 |
| Pulmonary vascular congestion (*x*-ray) | Yes | 7 | 129±76 | 8 | 95±44 |
| | No | 8 | 78±41 | 9 | 85±46 |
| Basal crepitations and/or 3rd heart sound | Yes | 10 | 114±68 | 11 | 83±35 |
| | No | 5 | 77±50 | 6 | 106±58 |
| Ventricular ectopic beats | Yes | 8 | 115±81 | 9 | 92±48 |
| | No | 7 | 86±34 | 8 | 89±37 |
| Norris index | >6·5 | 7 | 114±84 | 8 | 95±45 |
| | <6·5 | 8 | 88±42 | 9 | 87±42 |
| Peel index | >10 | 9 | 107±78 | 10 | 93±45 |
| | <10 | 6 | 95±47 | 7 | 89±41 |

estimated by the Peel index or the Norris index (Fig. 3).

The ΣST on day 1 failed to predict haemodynamic or arrhythmic complications during the subsequent hospital course (Table 1), or physical capacity (NYHA classification) among the survivors at 6 weeks after infarction.

## Comparison with peak and cumulated serum CK

ΣST on day 1 correlated approximately with the peak of the 2-hourly and the routine daily serum enzyme estimations (r=0·69, 0·68, respectively), as did $\Sigma\overline{ST}$ (r=0·61, 0·52, respectively) (see Table 2). These correlations were significant ($P < 0·05$) but there was a wide individual scatter (Fig. 4). The cumulated CK did not correlate with ΣST on day 1 or $\Sigma\overline{ST}$. The area of ST segment elevation (NST) did not correlate with any of the serum enzyme parameters.

## Trends in ΣST compared with trends in serum CK

Daily praecordial ST segment maps were compared with CK estimations in 38 patients. In 3 patients re-elevation of ΣST occurred: on one occasion there was an associated re-elevation in serum enzyme levels indicating reinfarction, but in 2 patients no change in serum enzymes resulted (Fig. 5).

Conversely, changes in serum enzyme levels measured every 2 hours indicated significant reinfarction in 2 patients, but the praecordial ST segment map failed to show any change in the ΣST or NST. A striking example is seen in Fig. 6.

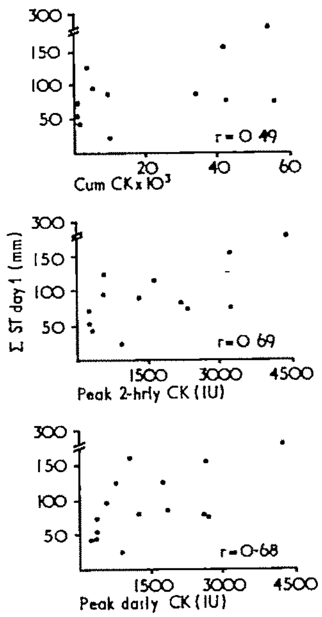

FIG. 4 *Correlation between ST on day 1 with enzymatic indices of necrosis. (Cum. CK=cumulated CK derived from Shell* et al., *1971).*

## Comparison of 42 lead and 12 lead electrocardiogram

ΣST calculated from 42 praecordial leads correlated well (r=0·90) with ΣST calculated from the 6 praecordial leads (V1–V6) of a standard electro-

TABLE 2 *Coefficient of correlation between ST segment elevation parameters and indices of clinical severity and serum enzyme estimations (NS=not significant)*

| | *ΣST day 1 (n=15)* | *$\Sigma\overline{ST}$ (n=17)* | *NST day 1 (n=15)* | *$\overline{NST}$ (n=17)* |
|---|---|---|---|---|
| Norris index (n=17) | 0 01<br>(NS) | 0·22<br>(NS) | −0·18<br>(NS) | −0·52<br>(NS) |
| Peel index (n=17) | 0 41<br>(NS) | −0·01<br>(NS) | 0·05<br>(NS) | −0·18<br>(NS) |
| Cumulated CK (n=15) | 0·49<br>(NS) | 0 41<br>(NS) | 0·357<br>(NS) | 0·08<br>(NS) |
| Peak 2-hour CK (n=15) | 0 69<br>(P<0·05) | 0 61<br>(P<0·05) | 0 43<br>(NS) | 0·304<br>(NS) |
| Peak daily CK (n=17) | 0·68<br>(P<0 01) | 0 52<br>(P<0·05) | 0 34<br>(NS) | 0 14<br>(NS) |

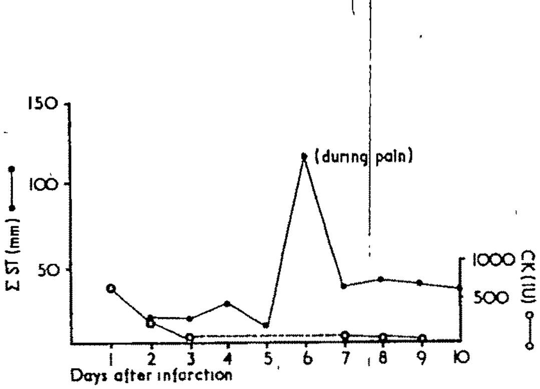

FIG. 5 *A 62-year-old-man with acute anterior myocardial infarction. On 6th hospital day, chest pain was associated with gross elevation of ST segments; subsequent serum enzyme estimations showed no rise.*

cardiogram and the trends in ΣST estimated by the two methods closely paralleled each other.

## Discussion

This study shows that the extent and amplitude of ST segment elevation detected in the praecordium is a poor indicator of the *extent* of myocardial necrosis; there was only a poor correlation between ST segment changes and serum enzyme release, the peak of two hourly or daily serum enzyme levels, and no correlation with several indices of clinical severity or clinical state at six weeks.

More significantly, these findings cast doubt on the assumption (Maroko *et al.*, 1972, 1973; Reid *et al.*, 1973, 1974; Braunwald and Maroko, 1974) that changes in ST segments detected by praecordial mapping will reflect *trends* in the extent of human myocardial injury. There was a wide day-to-day variation in individual patients and secondary rises in ST segments were not always corroborated with other evidence of reinfarction, such as changes in serum enzyme levels. In several patients, extension of necrosis which was obvious on sequential serum enzyme estimations was not detected in the daily ST segment maps performed in this study. Though it is conceivable that transient ST segment elevation may have occurred between praecordial maps performed each morning, our findings (Fig. 1) and those of others (Madias, Venkataraman, and Hood, 1975; Mills *et al.*, 1975) indicate that when ST segment elevation does accompany significant myocardial necrosis, it is sufficiently persistent to be detected within 24 hours after the event. Our findings showed an unacceptable disparity between ST segment elevation and serum levels of enzymes known to reflect myocardial necrosis. While serum creatine kinase elevation has been shown to reflect myocardial necrosis in patients dying of myocardial infarction (Mathey *et al.*, 1975), no such evidence validating ST segment elevation as an index of human myocardial necrosis has been presented.

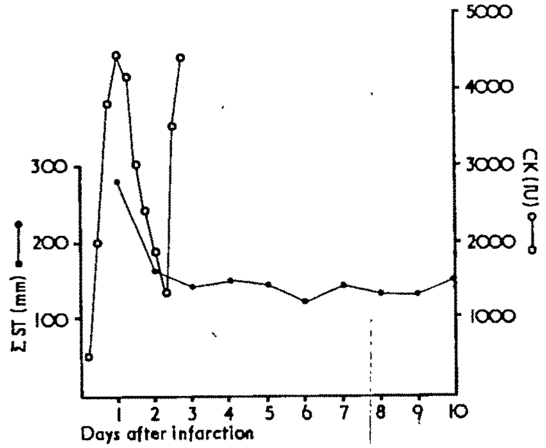

FIG. 6 *A 52-year-old man with extensive antero-lateral myocardial infarction. On 2nd hospital day, recurrence of chest pain was associated with gross re-elevation of serum CK; praecordial mapping failed to show re-elevation of ST segments.*

The extensive experimental work which has shown the relation of ST segment elevation to myocardial necrosis (Maroko *et al.*, 1971, 1972) has been performed in dogs with normal myocardium and localized coronary artery obstruction. When applied to patients with atherosclerotic heart disease who have suffered acute myocardial infarction it appears to measure phenomena that do not necessarily reflect myocardial necrosis. It is evident in the light of current attempts to limit infarct size (Braunwald and Maroko, 1974) that interventions cannot be evaluated solely by changes in praecordial ST segment mapping and will need to be combined with other methods which provide a more accurate measurement of myocardial necrosis (Sobel *et al.*, 1972; Norris *et al.*, 1975).

The possible prognostic significance of persistent ST segment elevation in identifying high risk patients for late sudden death (Wilson and Pantridge, 1973) or those unsuitable for early mobilization (Morris *et al.*, 1974) may indicate a possible role for the measurement of ST segment elevation. However, our findings suggest that there is no additional benefit in constructing a 42 lead ST segment map over measurement of the ST segments in the chest leads of the conventional 12 lead tracing.

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# Effect of potassium-sparing diuretics on the renin-angiotensin-aldosterone system and potassium retention in heart failure

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*The renin-angiotensin-aldosterone system and electrolyte levels in 11 patients with heart failure controlled on digoxin and frusemide were investigated after separate periods of Slow K, spironolactone, and amiloride therapy. When spironolactone or amiloride replaced Slow K, distinct parallel increments in the levels of renin, angiotensin II, and aldosterone resulted. Though plasma potassium was generally higher after spironolactone and amiloride than after Slow K, exchangeable potassium was similar with the three regimens. There was no significant relation between plasma potassium and concurrent exchangeable potassium.*

Total body potassium tends to be low in patients with cardiac failure (Singh, Hurley, and North, 1969; White *et al.*, 1969), and hypokalaemia is a frequent complication of conventional diuretic therapy in these patients (Sandoe and Olesen, 1962). Supplements of potassium are, therefore, advocated but doubt remains as to their efficacy (Down *et al.*, 1972). More recently, other potassium-sparing agents, such as spironolactone and amiloride have been promoted as means of conserving potassium, but these drugs have not yet been proved clearly superior in increasing body potassium. One reason for this could be the development of hyperaldosteronism, since in addition to any effect on plasma potassium concentration both amiloride and spironolactone are natriuretic and may further increase aldosterone secretion by augmenting renin and angiotensin production.

These relations have been explored in the present study in which the comparative effects of spironolactone, amiloride, and potassium supplements on the renin-angiotensin-aldosterone system have been studied together with changes in plasma, urine, and exchangeable potassium in 11 patients receiving maintenance diuretic therapy for congestive cardiac failure.

## Methods

Eleven patients, ages 33 to 73 years, were studied (Table) after obtaining informed consent. All had previously been treated for congestive heart failure with conventional glycoside and diuretic treatment and were free from oedema at the time of admission to the study. After discharge from hospital, all but 2 patients received potassium supplements in the form of Slow K for at least 4 weeks (range 4 weeks to 3 years). The patients continued to take digoxin (0·0625 to 0·75 mg daily in different patients) and frusemide (40 to 160 mg/d) at a constant dose, chosen by clinical criteria, for the duration of the study. Spironolactone or amiloride were substituted for Slow K at intervals of 2 months in each patient. In 4 patients amiloride was given first followed by spironolactone while in 5, spironolactone treatment preceded amiloride (see Table). Two patients (Cases 1 and 3) received treatment with only one potassium-sparing diuretic (spironolactone). Doses of potassium supplements (24 to 48 mmol/day), amiloride (10 to 15 mg/day), and spironolactone (100 mg/day) were chosen on clinical grounds and were held constant in any one patient for each treatment period. These details together with other essential drug therapy taken by the patients throughout the study are listed in the Table.

After each treatment period, the patient was admitted to hospital for 26 hours and measurements

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TABLE *Clinical, electrolyte, and treatment data*

| *Case No.* | *Sex* | *Age (y)* | *Body weight (kg)* | *Aetiology of heart failure* | *Other disorders* | *Frusemide dose (mg/day)* | *Assessment of dietary electrolyte intake (mmol/d)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Sodium* | *Potassium* |
| 1 | M | 57 | 66·4 | Ischaemic heart disease; chronic airways disease‡ | — | 160 | 63 | 62 |
| 2 | M | 73 | 57·2 | Ischaemic heart disease | — | 80 | 180 | 77 |
| 3 | M | 72 | 68·5 | Ischaemic heart disease | — | 120 | 126 | 45 |
| 4 | M | 55 | 101·4 | Idiopathic cardiomyopathy | Gout | 80 | 129 | 59 |
| 5 | F | 33 | 82·6 | Idiopathic cardiomyopathy | Obesity | 80 | 120 | 55 |
| 6 | M | 73 | 70·8 | Ischaemic heart disease | Diabetes mellitus | 40 | 116 | 60 |
| 7 | M | 60 | 83·2 | Ischaemic heart disease | — | 40 | 50 | 38 |
| 8 | M | 46 | 99·6 | Alcoholic cardiomyopathy | Chronic airways disease; obesity | 160 | 120 | 90 |
| 9 | M | 68 | 73·8 | Ischaemic heart disease; chronic airways disease | — | 80 | 110 | 66 |
| 10 | M | 54 | 97·2 | Ischaemic heart disease | Hypertension; gout; obesity; diabetes mellitus | 80 | 165 | 96 |
| 11 | F | 64 | 87·8 | Ischaemic heart disease | Obesity; diabetes mellitus, hyperthyroidism | 80 | 50 | 40 |

*In addition to digoxin, frusemide, and a potassium-sparing agent.
†Mean of two estimations in most cases: determined while receiving Slow K therapy.
‡Severe airways disease with $CO_2$ retention.

of exchangeable potassium and plasma volume were made. In addition, blood was drawn at 8 a.m. (overnight supine), 9 a.m. (after one hour of upright posture), 12 noon, 4 p.m., and 8 p.m. (free posture) for measurement of plasma renin activity (PRA) (Haber *et al.*, 1969), angiotensin II (AII) (Nicholls and Espiner, 1975), aldosterone (Ito *et al.*, 1972), and sodium and potassium. Simultaneous samples for cortisol determination (Murphy, 1967) were drawn in 8 of the 11 patients. Twenty-four-hour urinary electrolytes, creatinine and aldosterone (Bayard *et al.*, 1970) excretion were measured in urines collected on the day before, as well as on the day of hospital admission. In addition, full clinical assessment of cardiac status, chest *x*-ray, electrocardiogram, and measurements of creatinine clearance were carried out at the completion of each treatment period.

For the determination of exchangeable potassium ($K_E$) a precisely measured quantity (approximately 100 μCi) of $^{42}$K was given orally and the $K_E$ was calculated (Belcher and Vetter, 1971) from specific activity determined in a urine sample obtained 24 to 25 hours after the isotope's administration. Plasma volume was determined using $^{125}$I-labelled albumin. Normal values in this laboratory for subjects on unrestricted diets are as follows: 9 a.m. ambulant PRA 0·46 to 2·31 nmol/l per hr (600 to 3000 pg/ml per hr), AII 19 to 79 pmol/l (20 to 83 pg/ml), and plasma aldosterone 0·14 to 0·56 nmol/l (5 to 20 ng/100 ml); plasma cortisol 0·14 to 0·84 μmol/l (5 to 30 μg/100 ml); urine aldosterone excretion 13·9 to 50 nmol/d (5 to 18 μg/d). During the study, the patients were on an unrestricted diet which was not altered during the hospital admission. Each patient's electrolyte intake was assessed at least once during the study by a dietitian.

Statistical analyses (correlation coefficients and paired t-tests) were made using a Hewlett-Packard 9810A calculator.

## Results

### General

General health and cardiac status of all patients remained unchanged throughout the study period except in Case 9 who developed an exacerbation of cardiac failure while receiving spironolactone and in Case 1 who died suddenly shortly after starting amiloride. One patient (Case 3) withdrew from the study because he considered his health optimal on spironolactone.

Body weight was lower after spironolactone (mean fall 1·4 kg) and amiloride (mean fall 1·3 kg) compared to body weight measured after potassium supplements, but the differences were not significant ($P > 0·5$). *Plasma creatinine* and *creatinine clearance* were not significantly altered by any of the treatment regimens. *Plasma urea,* however, was higher after spironolactone (mean 47 ± 4·1 SEM mg/100 ml) than Slow K therapy (mean 31 ± 5·1 $P < 0·05$) or amiloride (mean 38·7 ± 2·8 $P > 0·2$). Venous *p*H,

| *Treatment schedules for Slow K (K), spironolactone (S), and amiloride (A)* | *Additional medication** | *Creatinine clearance (ml/min)†* |
|---|---|---|
| K, S | Chlordiazepoxide; nitrazepam, prednisone | 61 |
| K, S, A | — | 85 |
| K, S | Phenindione; quinalbarbitone | 45 |
| K, S, A | Quinidine; allopurinol | 158 |
| K, A, S, K | — | 95 |
| K, A, S | Nitrazepam | 73 |
| K, A, S | — | 85 |
| K, S, A | — | 178 |
| K, S, A | — | 74 |
| S, A, K | α-methyldopa, allopurinol, phenformin | 79 |
| A, S, K | Tolbutamide, carbimazole, indomethacin | 88 |

bicarbonate, and total $CO_2$ concentration were not significantly altered in any treatment regimen.

### Renin-angiotensin-aldosterone system

PRA, AII, and plasma aldosterone levels were mostly within normal limits after Slow K therapy, but were clearly increased by amiloride and spironolactone (Fig. 1). Proportionate changes in PRA, AII, and plasma aldosterone were seen within each treatment group. For all three hormones, the 9 a.m. upright value was significantly higher after the potassium-sparing diuretics than that seen after Slow K therapy ($P<0{\cdot}01$). The 9 a.m. upright PRA and AII values after treatment with spironolactone were significantly higher ($P<0{\cdot}05$ and $P<0{\cdot}01$, respectively) than those measured after amiloride, but the difference in plasma aldosterone failed to attain significance. That the lower hormone values after Slow K therapy were not dependent on the order of drug regimen used is shown by the similarity of findings in Cases 10 and 11 in whom Slow K therapy was the final treatment administered. Further, as shown in Fig. 2, reinstitution of Slow K therapy after potassium-sparing diuretics in Case 5 was accompanied by decrements in hormone concentrations to values observed initially. When hormone interrelations were analysed from the 5 plasma samples drawn on each hospital admission, PRA and AII levels were closely correlated in individual patients (range of r values 0·72 to 0·96, $P<0{\cdot}01$ to $P<0{\cdot}001$, $n=10$ to 15) and for the group as a whole ($r=0{\cdot}75$ $P<0{\cdot}001$, $n=154$). Likewise, fluctuations in AII and plasma aldosterone were statistically related overall ($r=0{\cdot}72$, $P<0{\cdot}001$, $n=154$) and in individuals ($r=0{\cdot}60$ to 0·95, $P<0{\cdot}02$ to $P<0{\cdot}001$, $n=10$ to 15) except in one patient (Case 2) where statistical significance was not achieved ($P>0{\cdot}05$). Plasma cortisol levels were, with few exceptions, within the normal range, and a diurnal pattern (highest level at 8 a.m. lowest at 8 p.m.) was usually seen. There was no correlation between concurrent plasma cortisol and aldosterone levels in 6 subjects ($P>0{\cdot}05$), though in 2 others the r values (0·54, 0·79) were significant ($P<0{\cdot}05$).

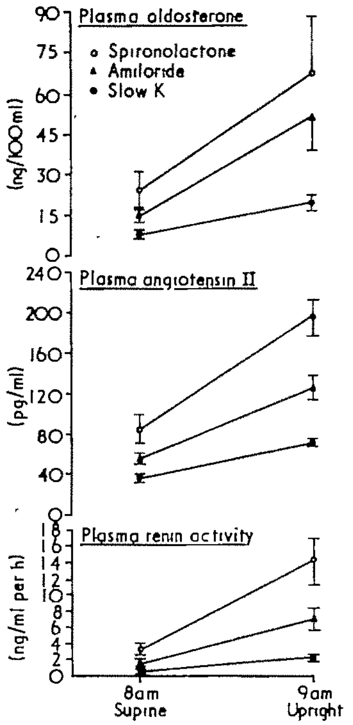

FIG. 1 *Plasma aldosterone, angiotensin II, and PRA values (mean ± standard error of the mean) in 11 patients receiving potassium-sparing drug regimens. 8 a.m. (overnight supine) and 9 a.m. (1 hour of upright posture) levels are shown. Conversion factors are: for plasma aldosterone 1 nmol/l = 36 ng/100 ml; PRA 1 nmol/l per hr = 1·3 ng/ml per hr; angiotensin II 1 pmol/l = 1·05 pg/ml.*

Urine aldosterone excretion reflected the changes observed in plasma hormone concentrations. After Slow K therapy, urine aldosterone was within normal limits (mean 25, range 11 to 50 nmol/day)

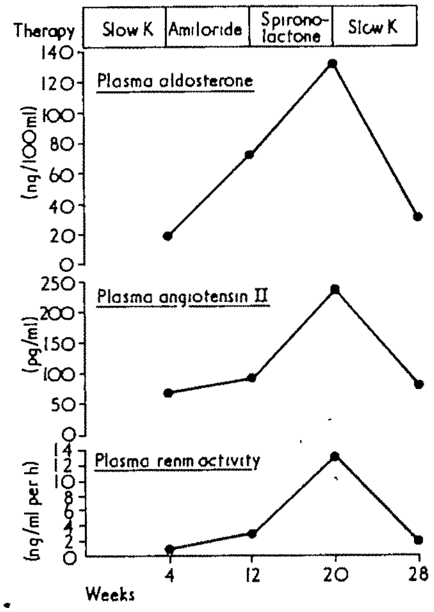

FIG. 2 *Plasma aldosterone, angiotensin II, and PRA in Case 5 after three different potassium-sparing drug regimens. Potassium supplements were administered on two different occasions, at the beginning and end of the study. Values shown are the mean of 5 estimations. See legend for Fig. 1 for conversion to SI units.*

but was increased by amiloride (mean 64, range 31 to 125 nmol/day) and by spironolactone (mean 75, range 33 to 167 nmol/day).

## Electrolyte levels

Changes in plasma potassium and sodium concentration, urine sodium/potassium ratio, and exchangeable potassium are shown for each of the 3 treatment periods in Fig. 3. Compared with levels after Slow K therapy, plasma potassium was higher after spironolactone ($P<0\cdot05$) but the increments seen after amiloride failed to achieve significance ($P>0\cdot2$). Plasma sodium fell after spironolactone ($P<0\cdot025$) and both spironolactone and amiloride caused an appreciable increase in the urine Na/K ratio ($P<0\cdot05$), in comparison with Slow K therapy. Despite these changes in the urine Na/K ratio and in plasma potassium, no significant change in $K_E$ was seen after treatment with either amiloride or spironolactone. Values for $K_E$ were usually within the reported normal range (Flear *et al.*, 1966), though 2 patients (Cases 3 and 7) had low values. $K_E$ after Slow K (mean 2905, range 2170 to 4413 mmol) was altered variably and insignificantly by spironolactone (mean 2715, range 1759 to 4109 mmol) and amiloride (mean 2864, range 1985 to 3815 mmol). Comparison of $K_E$ values according to body weight or height (Fig. 3) or on the basis of body surface area likewise indicated no significant difference between the three treatment regimens ($P>0\cdot2$). For the group as a whole, there was no significant correlation between mean plasma potassium and concurrent $K_E$ values ($r=0\cdot03$). However, dietary potassium intake (as assessed by a dietitian) was significantly related to the mean $K_E$ value for each patient ($r=0\cdot60$, $P<0\cdot02$). $K_E$ did not correlate with either frusemide dosage or with the level of urine or plasma aldosterone ($P>0\cdot2$).

Plasma volume measured after Slow K therapy (mean 3·2 ± 0·2 SEM litres) was not significantly altered by substitution with either spironolactone (mean 3·1 ± 0·2 SEM litres) or amiloride (mean

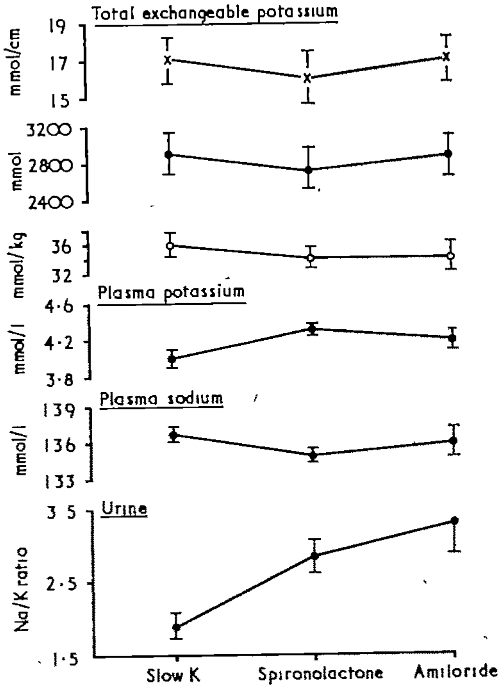

FIG. 3 *Total body exchangeable potassium and electrolyte values measured concurrently after potassium supplements, spironolactone, and amiloride in 11 patients with cardiac failure. For exchangeable potassium, levels are shown according to body weight (mmol/kg) and body height (mmol/cm) in addition to total body potassium. Mean ± SEM values are shown.*

3·3 ± 0·2 SEM litres) ($P > 0·4$). No relation between plasma volume and either PRA-AII concentrations (determined on the same day), or the dosage of frusemide, was found in this study.

## Discussion

These results show that significant hyperaldosteronism occurs in patients with heart failure when potassium-sparing diuretic drugs are added to conventional drug therapy. Hormone levels were unremarkable before the addition of amiloride or spironolactone despite doses of frusemide up to 160 mg daily. Since previous studies (Espiner *et al.*, 1969; Nicholls *et al.*, 1974) have shown that hyperaldosteronism frequently occurs towards the end of the diuretic phase in oedematous patients receiving frusemide, it appears that 'adaptation' of the renin-angiotensin system may occur with maintenance frusemide therapy, similar to that described in hypertensive patients receiving chronic diuretic therapy (Bourgoignie, Catanzaro, and Perry, 1968). Throughout the study, a close relation was observed between PRA and AII, and both of these indices were significantly correlated with plasma and urine aldosterone. While the increment in plasma potassium may also have contributed to aldosterone hypersecretion during spironolactone therapy, this was not likely after amiloride which at the doses used did not significantly raise plasma potassium.

From the cortisol data, ACTH did not dictate the observed aldosterone fluctuations. These findings, therefore, are consistent with a dominant role for AII in the control of aldosterone in patients treated with diuretics. Hitherto increases in plasma AII have been regarded important only in so far as they affect aldosterone and electrolyte metabolism. The recent demonstration that AII may contribute to myocardial necrosis in experimental animals (Gavras *et al.*, 1975) brings an additional note of caution, particularly in view of the very high levels of AII produced in some of our patients who had impaired myocardial function.

Whether the raised levels of renin, AII, and aldosterone would be sustained after more prolonged treatment with amiloride or spironolactone, cannot be confidently predicted from the current work. Nevertheless, the fact that the hormone levels were clearly increased after concurrent two-month periods of treatment with these 2 agents supports a long-term stimulatory effect of amiloride and spironolactone on the renin-angiotensin-aldosterone system.

Although clear-cut increases in the urine sodium/potassium ratio after both amiloride and spironolactone and in plasma potassium after spironolactone were seen in our patients, there was no significant alteration in $K_E$. The expression of $K_E$ in terms of body weight or height did not alter this conclusion. Previous studies in heart failure patients, though showing an improvement in plasma potassium in most cases (Friis, 1972; Croxson, Neutze, and John, 1972; Davidson and Gillebrand, 1973; Carney, Wilson, and Morgan, 1974), have variously reported increases (Friis, 1972; Carney *et al.*, 1974), or no change (Croxson *et al.*, 1972; Davidson and Gillebrand, 1973) in $K_E$ during therapy with potassium-sparing diuretics. It is possible that more prolonged therapy might shown increases in $K_E$, but this is not supported by our study when comparison was made between $K_E$ before and after two successive two-month potassium-sparing drug treatments. The development of hyperaldosteronism may possibly limit potassium conservation in amiloride-treated patients, but this seems unlikely with spironolactone where the drug competes with aldosterone at the receptor site—as indicated by the sustained increase in both plasma potassium and in the urine sodium/potassium ratios observed in our patients. In common with other studies (Croxson *et al.*, 1972; Flear, Cooke, and Quinton, 1957; De Deuxchaisnes *et al.*, 1961), there was no correlation of plasma potassium with $K_E$. However, a significant correlation of mean $K_E$ was found with the estimated dietary potassium intake. Details of the influence of plasma potassium concentration and of total body potassium upon myocardial function and on the risk of complications from digitalis therapy in heart failure patients remain to be clarified.

In conclusion, the addition of conventional doses of spironolactone or amiloride to diuretic treatment in patients with congestive heart failure did not alter $K_E$ but induced significant hyperaldosteronism. Aldosterone hypersecretion was more significantly related to hyper-reninism than to potassium retention.

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# Sustained haemodynamic action of nitroglycerin ointment[1]

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*Intravenous vasodilators have been shown to improve the haemodynamic status of patients in congestive heart failure. However, neither intravenous nor sublingual preparations are suitable for chronic administration or use in ambulatory patients In this study, nitroglycerin ointment was administered to 11 patients in congestive heart failure. Mean pulmonary wedge and arterial pressures, as well as systemic blood pressures and heart rate were then monitored for 2 to 5 hours and compared with baseline values. Pulmonary wedge and arterial pressures, as well as systemic systolic arterial pressure, decreased significantly at 15 minutes after application and remained depressed for up to 5 hours. Systemic diastolic pressures fell significantly at 30 minutes and also remained significantly reduced for up to 5 hours. Thus, nitroglycerin ointment may be suitable for chronic vasodilator therapy of congestive heart failure.*

Acute administration of systemic vasodilating drugs has been shown to improve the haemodynamic status of patients in congestive heart failure, with and without acute myocardial infarction (Miller *et al.*, 1975; Flaherty *et al.*, 1975; Shell and Sobel, 1974; Walinsky *et al.*, 1974). The nitrates and phentolamine have in fact been effective in some patients refractory to conventional therapy (Guiha *et al.*, 1974; Gold, Leinbach, and Sanders, 1972; Majid, Sharma, and Taylor, 1971).

Most studies to date have used potent, rapid acting intravenous preparations of sodium nitroprusside, nitroglycerin, phentolamine, or trimethaphan. These require intensive haemodynamic monitoring and precise control of infusion rates to avoid induction of dangerous systemic hypotension (Guiha *et al.*, 1974; Walinsky *et al.*, 1974). This manner of administration is necessarily restricted to the intensive care setting. More general clinical applicability would require a long-acting vasodilator preparation suitable for administration without intravenous infusion or frequent haemodynamic monitoring. Oral nitrate preparations have been proposed for this purpose (Franciosa *et al.*, 1974; Kasparian *et al.*, 1975), but controversy persists regarding their efficacy and resistance to rapid hepatic transformation (Goldstein *et al.*, 1971; Needleman, Lang, and Johnson, 1972).

Cutaneously administered nitroglycerin has the theoretical advantage of enhanced bioavailability because of direct absorption into the systemic circulation. It is similar in this regard to sublingual and intravenous preparations whose activity is readily seen but of brief duration (Goldstein *et al.*, 1971; Goldstein and Epstein, 1973; Klaus *et al.*, 1973). The cutaneous route might provide sustained activity on the basis of continuous absorption from a sizeable depot on the skin. In this connexion, nitroglycerin ointment has recently been shown to improve exercise tolerance in angina pectoris patients for at least 3 hours (Reichek *et al.*, 1974).

The present study was undertaken to determine whether nitroglycerin ointment causes nitrate-like haemodynamic effects of sufficient magnitude and duration to be of potential value in therapy of congestive heart failure.

## Methods

Eleven consecutive patients clinically suspected of having significant left ventricular dysfunction, and found to have pulmonary wedge pressures greater

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TABLE 1 *Biographical data and baseline haemodynamic values*

| *Case No.* | *Age (y)* | *Sex* | *Diagnosis* | *PWP (mmHg)* | *PAP (mmHg)* | *SSP (mmHg)* | *SDP (mmHg)* | *Heart rate (beats/min)* | *Dose of nitroglycerin ointment* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 63 | M | AMI | 28 | 39 | 111 | 80 | 92 | 5 cm, 2% |
| 2 | 62 | F | AMI | 20 | 25 | 153 | 100 | 96 | 2·5 cm, 2% |
| 3 | 75 | M | CAD | 40 | 51 | 135 | 100 | 120 | 5 cm, 2% |
| 4 | 40 | M | MHT | 24 | 25 | 173 | 125 | 80 | 2·5 cm, 2% |
| 5 | 49 | F | AMI | 14 | 19 | 174 | 101 | 94 | 2·5 cm, 2% |
| 6 | 49 | M | CAD | 21 | 29 | 116 | 81 | 70 | 2·5 cm, 2% |
| 7 | 58 | M | AMI | 23 | 30 | 142 | 97 | 86 | 2·5 cm, 2% |
| 8A* | 45 | M | CAD | 31 | 38 | 89 | 70 | 100 | 5·0 cm, 4% |
| 8B* | 45 | M | CAD | 36 | 40 | 79 | 60 | 92 | 5·0 cm, 2% |
| 9 | 32 | M | MHT | 19 | 33 | 212 | 131 | 66 | 5·0 cm, 2% |
| 10 | 74 | F | AR | 29 | 45 | 161 | 83 | 87 | 5·0 cm, 2% |
| 11 | 50 | M | AMI | 29 | 40 | 122 | 90 | 112 | 2·5 cm, 2% |
| Mean ± SEM | | | | 26 ± 2·2 | 34·5 ± 2·7 | 138·9 ± 11·1 | 93·2 ± 6·0 | 91·3 ± 4·5 | |

*Abbreviations:* AMI, acute myocardial infarction; CAD, chronic coronary arterial disease; MHT, malignant hypertension; AR, aortic valvular regurgitation; PWP, pulmonary wedge mean pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure.

*Same patient studied on two separate occasions.

than 14 mmHg were included in the study. Patients' age, sex, cardiac diagnosis, and control haemodynamic values are listed in Table 1. One patient was studied on two separate occasions at an interval of 10 days before and after ventricular aneurysmectomy. No patient was given digitalis for the first time on the day of study. No patient previously on digitalis received greater than a maintenance dose of a digitalis preparation on the day of study. Only intravenous frusemide was used for diuresis and this was not administered within 4 hours before entry into the study. Informed written consent was obtained from all patients before study. Right heart catheterization was performed at the bedside, using No. 7 French Swan-Ganz catheters (Swan *et al.*, 1970). Right heart pressures were measured, using an Ailtech Model M510 transducer and a Tektronix Model 412 pressure amplifier. Zero reference point was taken at the mid chest. Systemic systolic and diastolic pressures were measured by sphygmomanometry. Control values for pulmonary wedge pressure, pulmonary arterial pressure, systemic systolic and diastolic pressure, and heart rate were obtained twice at an interval of 30 minutes. No patient whose second control value for pulmonary wedge pressure was more than 5 mmHg below the first value or less than 14 mmHg was included in the study. Control values were taken as the average of both readings. Immediately after the second control reading, 2·5 cm 2 per cent nitroglycerin ointment was applied to a 232 cm$^2$ area of skin on the back or thighs and covered with an occlusive plastic dressing. Haemodynamic measurements were then made at 15-minute intervals. If no appreciable fall in pulmonary wedge pressure was seen within 30 minutes, a second 2·5 cm nitroglycerin ointment was applied to another 232 cm$^2$ area and measurements were repeated. If there was still no fall in pulmonary wedge pressure (Case 8A) the 2 per cent nitroglycerin ointment was removed and replaced by 5 cm 4 per cent nitroglycerin ointment applied to two separate 232 cm$^2$ areas. Once a fall of pulmonary wedge pressure >5 mmHg was observed, subsequent measurements were made at 30 to 60 minute intervals for 2 to 5 hours.

Control pressures and heart rates were expressed as mean ± standard error of the mean (SEM). The haemodynamic changes attributed to nitroglycerin ointment were expressed as mean differences from control values ± standard error of the difference (SED). Statistical evaluation was performed using Student's t test for paired data.

In view of the necessity to withhold inotropic or diuretic agents during the study period, use of a placebo ointment was considered unjustified.

## Results

Nitroglycerin ointment caused significant reductions in pulmonary wedge pressure, pulmonary arterial pressure, and systemic blood pressures that were maintained for up to 5 hours. Mean differences

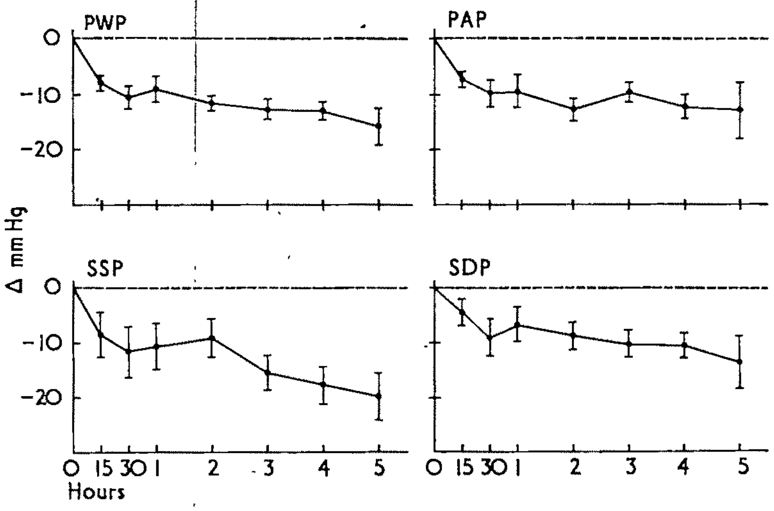

FIG. 1 *Haemodynamic changes after application of nitroglycerin ointment. Results as mean differences from baseline ± SED. PWP, pulmonary wedge mean pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure.*

from control for all values are listed in Table 2 and illustrated in Fig. 1.

Pulmonary wedge pressure was significantly reduced by 7·9 mmHg at 15 minutes ($P < 0{\cdot}005$). Maximum reductions of 12·9 mmHg and 15·8 mmHg occurred at 4 and 5 hours, respectively ($P < 0{\cdot}005$ for both).

Similary, pulmonary artery pressure was significantly reduced by 7·3 mmHg ($P < 0{\cdot}005$) at 15 minutes. Peak reductions were 12·1 mmHg and 12·9 mmHg at 4 and 5 hours ($P < 0{\cdot}005$ and $< 0{\cdot}05$).

Systemic systolic pressure was also significantly reduced at 15 minutes by 8·5 mmHg ($P < 0{\cdot}05$). Again, peak effect was observed at 4 and 5 hours when reductions were 17·7 mmHg and 19·8 mmHg, respectively ($P < 0{\cdot}005$ and $< 0{\cdot}025$).

The reduction in systemic diastolic pressure was not significant until 30 minutes and was 9·0 mmHg ($P < 0{\cdot}025$) at that time. Again, peak reductions of 10·5 mmHg and 13·5 mmHg were noted at 4 and 5 hours ($P < 0{\cdot}005$ and $< 0{\cdot}05$, respectively).

Five of six patients showed return of haemodynamic levels toward normal within one hour of removal of nitroglycerin ointment.

Although no attempt was made to quantify symptoms or physical signs, 4 patients who were dyspnoeic during the control period had relief of

TABLE 2 *Changes in haemodynamic parameters after administration of nitroglycerin ointment*

| | *15 min* | *30 min* | *1 hr* | *2 hr* | *3 hr* | *4 hr* | *5 hr* |
|---|---|---|---|---|---|---|---|
| PWP (mmHg) | ***<br>−7·9 ± 1·5 | ***<br>−10·6 ± 2·3 | ***<br>−9·0 ± 2·4 | ***<br>−12·5 ± 2·4 | ***<br>−12·7 ± 1·8 | ***<br>−12 9 ± 1·7 | **<br>−15 8 ± 3·3 |
| PAP (mmHg) | ***<br>−7·3 ± 1·5 | ***<br>−9·6 ± 2·5 | ***<br>−9·4 ± 2·9 | ***<br>−12·8 ± 2·1 | ***<br>−9·5 ± 1·7 | ***<br>−12·1 ± 2·1 | *<br>−12·9 ± 5·1 |
| SSP (mmHg) | *<br>−8·5 ± 4·2 | **<br>−11·6 ± 4 6 | **<br>−10·8 ± 4·2 | **<br>−9 0 ± 3·6 | ***<br>−15·3 ± 3·2 | ***<br>−17·7 ± 3·4 | **<br>−19·8 ± 4·3 |
| SDP (mmHg) | −4·4 ± 2·4 | **<br>−9·0 ± 3·4 | *<br>−6·6 ± 3·2 | ***<br>−8·7 ± 2·5 | ***<br>−10·3 ± 2·4 | ***<br>−10·5 ± 2·4 | *<br>−13·5 ± 4·7 |
| HR (beats/min) | −0·8 ± 1·9 | −1·1 ± 3·5 | −2·9 ± 3 0 | −1·2 ± 3·8 | −0·3 ± 4·5 | −3·9 ± 3·6 | −8·5 ± 5·3 |
| No. of patients | 10 | 10 | 12 | 12 | 11 | 11 | 4 |

*Abbreviations :* PWP, pulmonary wedge pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure; HR, heart rate; *=$P<0$ 05; **=$P<0{\cdot}025$; ***=$P<0{\cdot}005$.

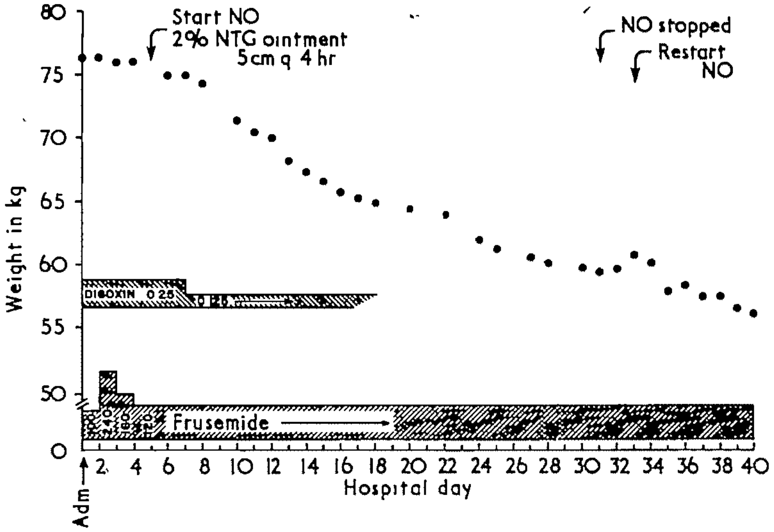

FIG. 2 *Daily weights in Case 10 with severe biventricular failure who was treated with maintenance nitroglycerin ointment (NO) in addition to digoxin and frusemide (see text).*

this symptom after nitroglycerin ointment was applied. A 74-year-old woman (Case 10) had severe biventricular failure and anasarca on the basis of aortic regurgitation. After 4 days of treatment with bed rest, sodium restriction, digoxin, and high doses of frusemide, she had lost only 0·45 kg. She was then admitted to this study and given 5 cm 2 per cent nitroglycerin ointment which reduced her pulmonary wedge pressure from 29 to 12 mmHg, and her dyspnoea improved. Subsequently, she was maintained on this dose of nitroglycerin ointment every 4 hours, as well as maintenance digoxin and frusemide, and had prompt onset of a sustained diuresis. Her daily weights and medicines given are plotted in Fig. 2. When nitroglycerin ointment was discontinued for 3 days she regained 1·8 kg. Weight loss then resumed when nitroglycerin ointment was reinstituted.

No patient developed symptoms or physical signs of systemic arterial hypotension during the study. Several patients complained of headache. One patient noted mild burning at the site of 4 per cent nitroglycerin ointment application.

## Discussion

The beneficial effects of sublingual or intravenous vasodilating drugs in congestive heart failure have been attributed to simultaneous reduction of left ventricular outflow impedance and filling pressure caused, respectively, by arteriolar and venous vasodilatation. These changes permit the left ventricle to operate at a smaller cavity size with consequently improved mechanical efficiency and reduced myocardial oxygen demand. The observed haemodynamic effects include distinct reduction in pulmonary wedge pressures and modest reduction in systemic arterial pressures without change in heart rate (Miller *et al.*, 1975; Gold *et al.*, 1972; Flaherty *et al.*, 1975; Franciosa *et al.*, 1972). Cardiac output response is variable and appears to be a function of left ventricular filling pressure (Miller *et al.*, 1975; Gold *et al.*, 1972; Johnson, Fairley, and Carter, 1959; Walinsky *et al.*, 1974; Williams, Amsterdam, and Mason, 1975). Since our intention was to examine the duration of action of nitroglycerin ointment, only those variables known to change unidirectionally in response to vasodilators were monitored, and cardiac output was not included.

In this study, administration of nitroglycerin ointment to patients with left ventricular dysfunction resulted in significant lowering of pulmonary wedge pressure, pulmonary arterial pressure, and systemic arterial pressures, characteristic of that seen with intravenous or sublingual vasodilators. Significant reductions were usually noted at 15 to 30 minutes after application and a significant effect persisted for up to 5 hours. Clinically important hypotension was not encountered. Though considerable individual variation was noted, average coronary perfusion pressure (estimated by subtraction of wedge pressure from systemic diastolic pressure) was not significantly decreased at any measured interval.

Not surprisingly, the size of the application area played a critical role in producing these haemodynamic effects. No appreciable haemodynamic changes were observed when smaller, 103 cm², application areas were used. Furthermore, about half of our subjects required a doubling of the initial dose and application area for achievement of an adequate response.

For the purpose of this study, reduction of pulmonary wedge pressure was used as an objective indicator of drug effectiveness. Our experience suggests that for routine use it would be sufficient to monitor systemic blood pressure while increasing the dose and application area until a satisfactory clinical response is observed. In this connexion, 3 of our study patients who were symptomatic and poorly responsive to conventional therapy for congestive heart failure were maintained on nitroglycerin ointment after the study. All reported improvement in their congestive symptoms, and untoward effects other than headaches were not observed. The clinical course in one patient with biventricular failure and anasarca has been described above and in Fig. 2.

The sustained haemodynamic activity observed in our study suggests that nitroglycerin ointment may prove applicable to other disease states for which vasodilator therapy is appropriate, such as in prophylaxis of angina pectoris. Though this study did not deal specifically with angina, our demonstration of sustained pharmacological activity is consistent with the exercise studies of Reichek *et al.* (1974).

Recent studies in both experimental animals and man suggest that vasodilator therapy during acute myocardial infarction may limit the extent and sequelae of myocardial necrosis (Flaherty *et al.*, 1975; Shell and Sobel, 1974; Smith *et al.*, 1973; Borer *et al.*, 1974). If future investigations confirm these findings, nitroglycerin ointment may provide a convenient means of reducing myocardial oxygen demand in routine management of acute myocardial infarction.

In summary, our data indicate that nitroglycerin ointment causes a sustained haemodynamic response similar to that seen with acutely administered vasodilators. With careful adjustment of dosage and application area it can be used in ambulatory patients without induction of dangerous hypotension. Accordingly, it has potential value in chronic vasodilator therapy of congestive heart failure and merits consideration for use in other clinical situations for which sustained vasodilatation is appropriate.

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# Haemodynamics after Mustard's operation for transposition of the great arteries[1]

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*Cardiac catheterization data from 54 investigations after Mustard's procedure were examined to study the influence of the operation on pressure events in the atria, great veins, and pulmonary circulation. Systemic venous atrial pressure tracings were characterized by a rapid, sharp 'y' descent. Pressure gradients between the venae cavae and systemic venous atrium were invariable, whether or not vena caval pathway obstruction was present, the 'y' trough and 'a' wave gradients being greater than the mean gradient. Pulmonary venous atrial pressure tracings were not different from normal except when tricuspid regurgitation was present. It is suggested that the baffle effectively reduces the size and compliance of the systemic venous atrium, but influences the pulmonary venous atrium to a lesser degree.*

*The systolic pressure gradient from the left ventricle to pulmonary artery was decreased postoperatively, suggesting that it may be flow-related; the greatest changes were seen in the group with preoperative ventricular septal defect. The ratio of pulmonary : systemic vascular resistance did not change significantly after operation, and it is suggested that both the pre- and postoperative values were higher than normal. Examination of the left ventricular or pulmonary arterial mean pressure postoperatively should raise the suspicion of a complication, e.g. pulmonary venous obstruction or tricuspid regurgitation.*

Since 1964, the physiological correction of transposition of the great arteries has been achieved by Mustard's operation in numerous patients. Several reports of postoperative studies have included both immediate and long-term results (Kidd and Mustard, 1966; Shankar *et al.*, 1967: Price *et al.*, 1971; Stark *et al.*, 1972; Rodrigues-Fernandez *et al.*, 1972; Morgan *et al.*, 1972; Rizk, Moller, and Amplatz, 1973; Newfeld *et al.*, 1974; Venables, Ediz, and Clarke, 1974; Stark *et al.*, 1974).

In Mustard's procedure an artificial baffle channels vena caval blood through the mitral valve into the left ventricle, and pulmonary venous blood through the tricuspid valve into the right ventricle. The present report considers the influence of the baffle on the pressure events in the atria and great veins, and the changes in the pulmonary vascular and left ventricular dynamics.

The importance of recognizing postoperative vena caval pathway obstruction has previously been stressed (Stark *et al.*, 1974). An examination of venous and atrial pressure events is fundamental to the understanding of this complication. Pulmonary vascular disease is well documented as an early complication of transposition of the great arteries (Ferguson, Adams and Watson, 1960; Noonan *et al.*, 1960; Ferencz, 1966; Viles, Ongley, and Titus, 1969; Mair *et al.*, 1971; Newfeld *et al.*, 1974). The importance of evaluating the pulmonary vascular resistance preoperatively has been stressed (Mair *et al.*, 1971; Newfeld *et al.*, 1974). An objective assessment of the postoperative pulmonary vascular dynamics is, therefore, relevant in determining the influence of preoperative values on the long-term result.

## Subjects and methods

Forty-eight of the 256 survivors of Mustard's operation performed between 1965 and 1974 have been studied by cardiac catheterization, 6 of them on 2 occasions. The age at operation ranged from 3 months to 20 years (median 28 months) and at re-

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investigation from 5 months to 25 years (median 47 months). The interval between the operation and the investigation ranged from 1 week to 6 years (mean 21 months, median 13 months). In all instances, there were clinical indications for cardiac catheterization. Some patients were investigated because they presented with the physical signs of vena caval pathway obstruction, of pulmonary venous obstruction, or of severe tricuspid regurgitation. Others were studied because one of these complications was suspected, because they were cyanosed, or because there was cardiac enlargement, usually with a loud systolic murmur.

Both the systemic and pulmonary venous sides of the heart were catheterized in 35 of the 54 studies but only the systemic venous side in the remaining 19. The systemic venous catheter was introduced via a convenient vein in either the upper or lower limb, and the systemic venous atrium and ventricle were entered easily from either the superior or inferior vena cava. It was usually easy to enter the pulmonary artery with a standard Lehman or Cournand catheter. Difficulties in manipulating the catheter through the systemic venous atrium post-

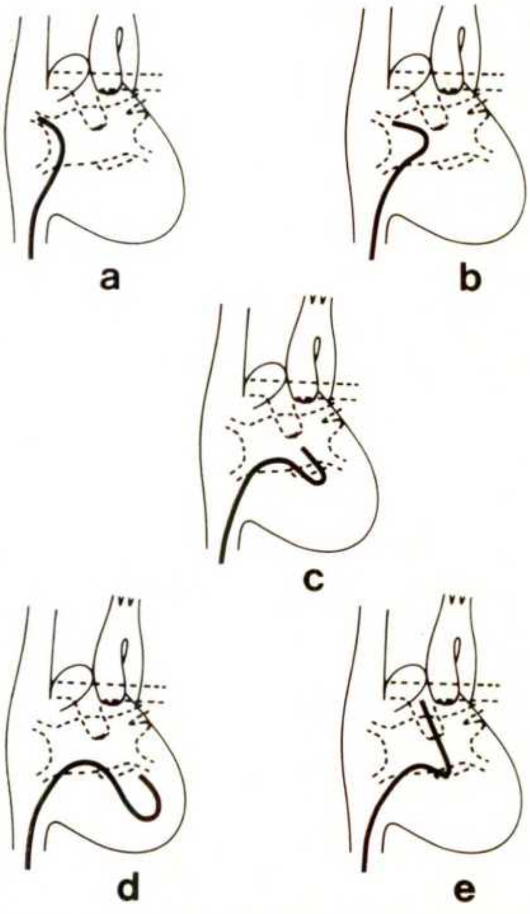

FIG. 1 *Catheterization of the pulmonary artery in transposition of the great arteries using a Goodale Lubin catheter. The catheter tip is positioned in the right upper pulmonary vein (a) and a loop formed (b). This loop is passed through the mitral valve (c) into the left ventricle and positioned so that the tip remains cranially directed, and the loop laterally directed (d). If the catheter is then withdrawn, the tip will pass into the pulmonary artery (e).*

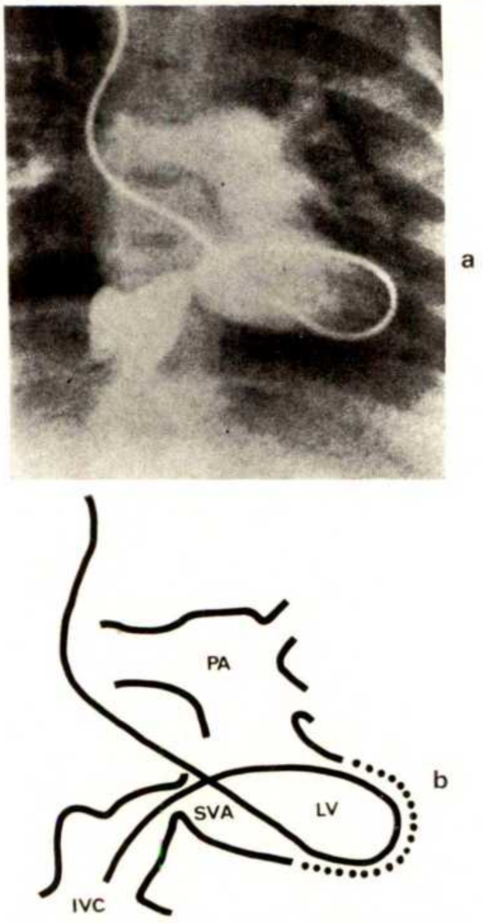

FIG. 2 *(a) Technique for catheterizing inferior vena cava (IVC) from superior vena cava (SVC) after Mustard's operation (see text). The loop of the catheter lies in the left ventricle (LV) and the tip has re-emerged from the mitral valve into systemic venous atrium (SVA) and inferior vena cava. There is some intracardiac inferior vena caval pathway obstruction. (b) Line drawing of Fig. 2 (a).*

operatively, and into the pulmonary artery preoperatively and postoperatively, were overcome by techniques illustrated in Fig. 1 and 2. The pulmonary venous atrium and most of the pulmonary veins were entered retrogradely from the aorta and right ventricle without difficulty.

In most instances, pressure and oxygen saturation were measured in the heart chambers, great arteries, and great veins. Pressures were measured with a fluid-filled catheter using Statham P23 Gb pressure transducers and a Mingograph 81 Recorder. Selective angiocardiography was performed as indicated (Stark *et al.*, 1972; Tynan, Aberdeen, and Stark, 1972; Stark *et al.*, 1974). The relevant findings from preoperative cardiac catheterization studies were available for comparison in almost all the patients who were restudied postoperatively.

With respect to the pulmonary vascular and left ventricular dynamics we have compared the following variables:

(1) Pulmonary arterial mean pressure ($P_{\overline{PA}}$).
(2) Left ventricular peak systolic pressure.
(3) Peak systolic pressure gradient between the left ventricle ($P_{LV}$) and pulmonary artery ($P_{PA}$). This was expressed as: (a) the absolute gradient and (b) the gradient in relation to flow ratio; thus, the postoperative gradient was compared with the preoperative index of:

$$\frac{P_{LV} - P_{PA}}{\dot{Q}_p/\dot{Q}_s}$$

where $\dot{Q}_p/\dot{Q}_s$ is pulmonary: systemic flow ratio derived from blood oxygen saturation data.

(4) Ratio of pulmonary: systemic vascular resistance ($R_p/R_s$). The preoperative ratio was calculated using the formula:

$$R_p/R_s = \frac{\dot{Q}_s \; (P_{\overline{PA}} - P_{\overline{LA}})}{\dot{Q}_p \; (P_{\overline{AO}} - P_{\overline{RA}})}$$

where $P_{\overline{PA}}$, $P_{\overline{LA}}$, $P_{\overline{AO}}$, and $P_{\overline{RA}}$ represent mean pressures in pulmonary artery, left atrium, aorta, and right atrium, respectively. The postoperative ratio was calculated in the same way except that the pulmonary venous atrial mean pressure was substituted for $P_{\overline{LA}}$ and the average of the vena caval mean pressures for $P_{\overline{RA}}$. $\dot{Q}_p/\dot{Q}_s$ was assumed to be unity in the absence of shunts, and for the purpose of these calculations, coronary sinus flow into the pulmonary venous atrium was ignored.

The above variables were analysed in the group as a whole and in subgroups with the following:

(a) Preoperative ventricular septal defect.
(b) Postoperative systemic venous pathway obstruction (Stark *et al.*, 1974).
(c) Postoperative tricuspid regurgitation (Tynan *et al.*, 1972).
(d) 'Simple' transposition of the great arteries with no postoperative complications. Preoperative and postoperative values of each variable were compared using the paired 't' test.

## Results

### (a) Superior and inferior vena caval and systemic venous atrial pressure

The systemic venous atrial pressure tracings had the usual waves and troughs but were characterized by a rapid, sharp 'y' descent coinciding with early ventricular diastole (Fig. 3, 4, 5). In 44 of the 54 cardiac catheterizations 'a' and 'v' waves and 'x' and 'y' troughs were identifiable; the 'y' trough was lower than the 'x' in all but two cases, the mean difference in pressures being 4 mmHg (0·5 kPa) (SEM ±0·5, $P < 0{\cdot}001$). Pressures in the superior and inferior vena cava were generally higher than in the systemic venous atrium whether or not the vena caval pathways were obstructed clinically (Table 1). This was true of the mean pressures and of the individual pressure waves and troughs. In both the obstructed and unobstructed groups the 'a' wave and 'y' trough gradients were significantly greater than the mean gradients (Table 1, Fig. 3, 4, 5).

As expected, the pressure gradients were usually greater when obstruction was present. Giant 'a' waves were seen in some superior vena caval pressure tracings (Fig. 3). In these cases, cineangiography showed intracardiac obstruction of the superior vena caval pathway and presystolic reflux of contrast material up the superior vena cava, which was attributed to contraction of the right atrial appendage, upstream to the obstruction.

### (b) Pulmonary venous atrial pressures

After Mustard's operation, the pulmonary venous atrium drains through the tricuspid valve into the right ventricle. Thus, the tricuspid valve has the same physiological function as the mitral valve in the normal circulation. The pulmonary venous atrial mean pressures did not differentiate between those patients who had grade 1 and 2 tricuspid regurgitation and those who did not ('Normals') (Table 2). The 'v' waves were significantly higher in the group with tricuspid regurgitation. In the 'Normals' there was no significant difference between the magnitudes of the 'a' and 'v' waves or between the 'x' and 'y' troughs. In patients with tricuspid regurgitation the 'v' waves were significantly higher than the 'a' (mean difference 8·6 mmHg (1·1 kPa), $P < 0{\cdot}01$) and the 'y' troughs were significantly lower than the

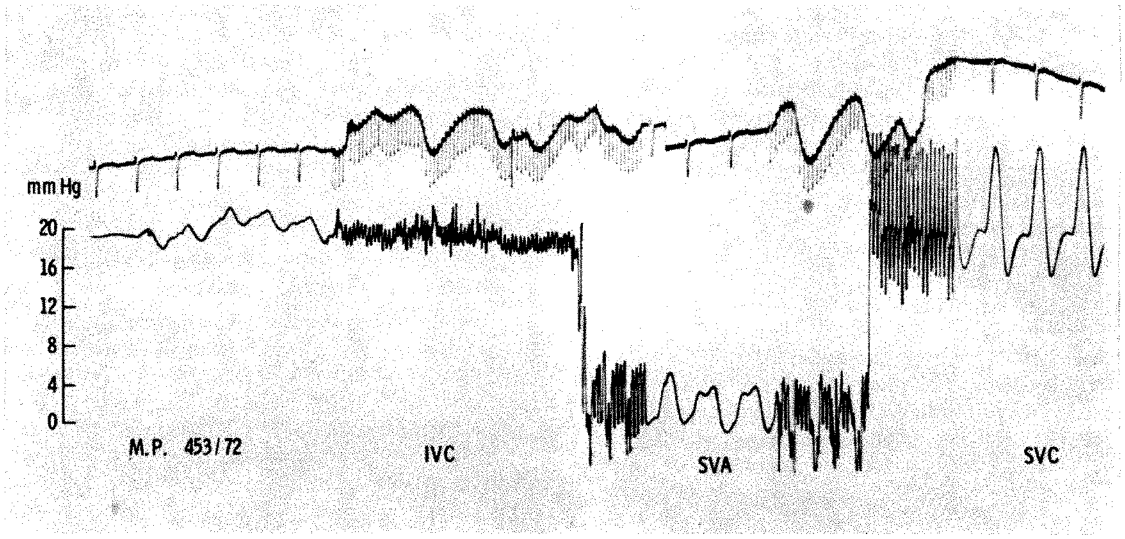

FIG. 3 *Withdrawal pressure tracing from inferior vena cava through systemic venous atrium (SVA) to superior vena cava (SVC) in patient with obstruction of both vena caval pathways. Note giant 'a' waves in superior vena caval (SVC) tracing and deep 'y' troughs in systemic venous atrium (SVA).*

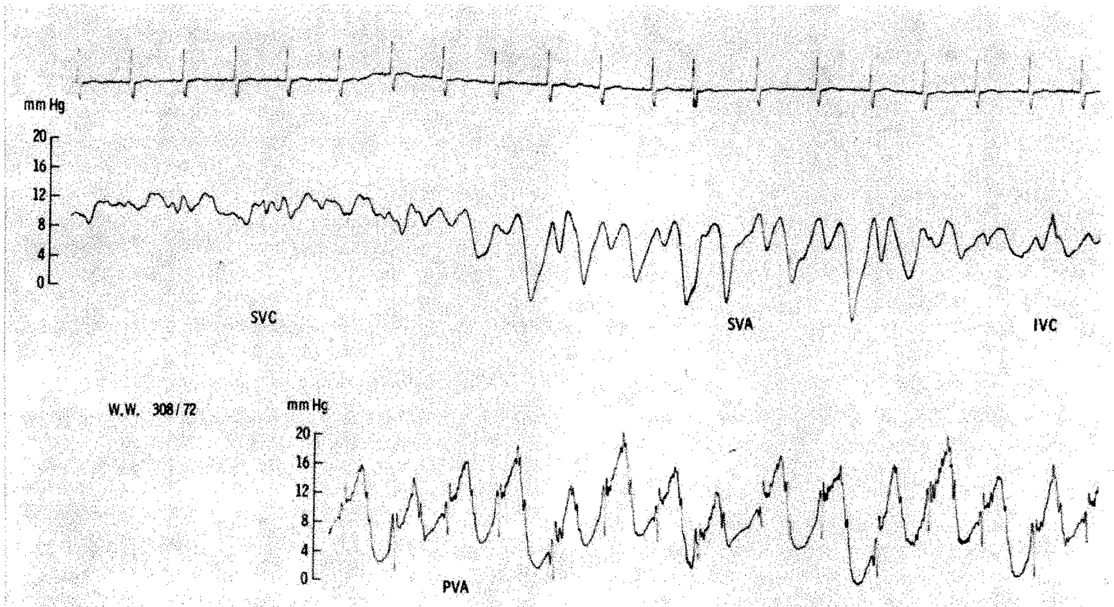

FIG. 4 *Simultaneous recording of pulmonary venous atrial (PVA) pressure and pressure during withdrawal from superior vena cava (SVC) through systemic venous atrium (SVA) to inferior vena cava (IVC). Patient has mild tricuspid regurgitation with dominant 'v' waves in pulmonary venous atrium. Note small pressure gradients from both superior vena cava and inferior vena cava to systemic venous atrium despite absence of clinical or angiographic evidence of vena caval pathway obstruction. Note also the dominant 'y' trough in systemic venous atrium but not in superior or inferior vena cava.*

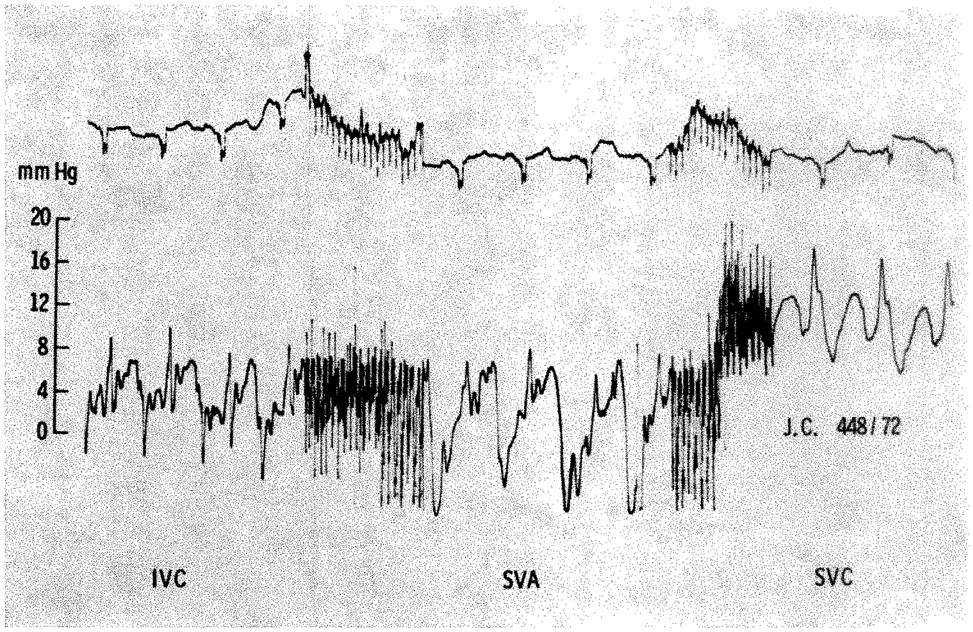

FIG. 5 *Withdrawal pressure tracing from inferior vena cava (IVC) through systemic venous atrium (SVA) to superior vena cava (SVC) in patient with superior vena caval pathway obstruction. Note 'y' trough in systemic venous atrium, absence of significant gradient between inferior vena cava and systemic venous atrium, and high superior vena cava pressure.*

'x' (mean difference 4·5 mmHg (0·6 kPa), $P < 0.001$) (Fig. 4). Thus in patients with tricuspid regurgitation the 'v' wave was the highest and the 'y' trough was the lowest in the pulmonary venous atrial pressure tracing. In 4 patients with severe tricuspid regurgitation, mean pulmonary venous atrial pressures were raised to a mean of 28 mmHg (3·7 kPa) (Tynan *et al.*, 1972).

Two of the patients in this study had pulmonary venous obstruction with mean pressure gradients of 10 and 30 mmHg (1·3 and 4·0 kPa) between the pulmonary veins and pulmonary venous atrium (Stark *et al.*, 1972). In all other patients with pulmonary venous pressure measurements, gradients were not present.

**(c) Pulmonary arterial mean pressure ($P_{\overline{PA}}$)**

Postoperative values for $P_{\overline{PA}}$ did not differ significantly from preoperative values in the whole group or in the subgroups with preoperative ventricular septal defect or postoperative systemic venous pathway obstruction. In the subgroup with moderate to severe tricuspid regurgitation, the postoperative $P_{\overline{PA}}$ tended to be higher than the preoperative

TABLE 1 *Pressure gradients between venae cavae and systemic venous atrium (SVA)*

| | *Pressure gradient (mmHg)** | | |
|---|---|---|---|
| | *Unobstructed* | *SVC obstructed* | *IVC obstructed* |
| SVC—SVA mean | 3·9 ± 1·8 (29) | 16·9 ± 9·0***(19) | |
| SVC—SVA 'a' wave | 3·1 ± 4·6 (26) | 20·3 ± 10·0***(16) | |
| SVC—SVA 'y' trough | 6·6 ± 3·1 (28) | 19·0 ± 8·9***(18) | |
| IVC—SVA mean | 1·3 ± 1·7 (23) | 5·4 ± 4·4**(14) | 17·8 ± 8·8***(5) |
| IVC—SVA 'y' trough | 3·7 ± 2·9 (22) | 7·6 ± 5·3**(14) | 20·6 ± 8·9***(5) |

*Average gradient ± 1 SD. No. of cases in parentheses.
Significance of differences between gradients in obstructed and unobstructed cases:
**$P < 0.01$.
***$P < 0.001$.

TABLE 2 *Pulmonary venous atrial pressures in patients with and without 'mild' tricuspid regurgitation*

| | *Pulmonary venous atrial pressure (mmHg)** | | |
|---|---|---|---|
| | *Mean* | *'v' wave* | *'v' minus 'a'* |
| No tricuspid regurgitation | 9·5 ± 5·0 (17) | 13·5 ± 6·4 (17) | 2·0 ± 4·6 (17) |
| 'Mild' tricuspid regurgitation (grade 1 or 2/4) | 11·5 ± 7·1 (16) | 21·5 ± 10·8 (16) | 8·6 ± 7·5 (12) |
| Significance of difference | NS | $P < 0{\cdot}02$ | $P < 0{\cdot}02$ |

*Average ± 1 SD. No. of cases in parentheses..

though the difference was not significant (mean preoperative $P_{\overline{PA}} = 19$ mmHg (2·5 kPa), mean postoperative $P_{\overline{PA}} = 33$ mmHg (4·4 kPa), $P > 0{\cdot}05$).

### (d) Left ventricular peak systolic pressure ($P_{LV}$)

The postoperative mean value for $P_{LV}$ did not differ significantly from the preoperative value in the whole group. In the subgroup with tricuspid regurgitation, the postoperative $P_{LV}$ was higher than the preoperative value but the difference was not significant. In the subgroup with preoperative ventricular septal defect, the $P_{LV}$ decreased postoperatively by a mean of 10 mmHg (Table 3). This was not significant.

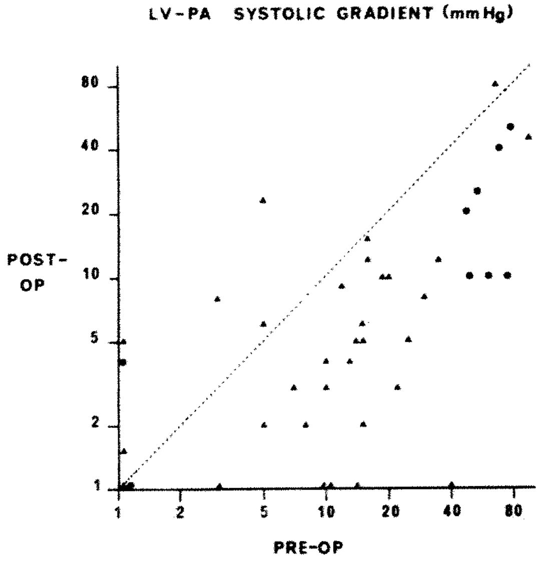

FIG. 6 *Systolic pressure gradient between left ventricle and pulmonary artery before and after Mustard's operation. For convenience of display, a logarithmic scale has been used in both axes. The solid triangles represent patients with 'simple' transposition of great arteries and the solid circles represent those with ventricular septal defects. The dotted line (line of identity) shows that in the majority of patients, the preoperative gradient was greater than the postoperative.*

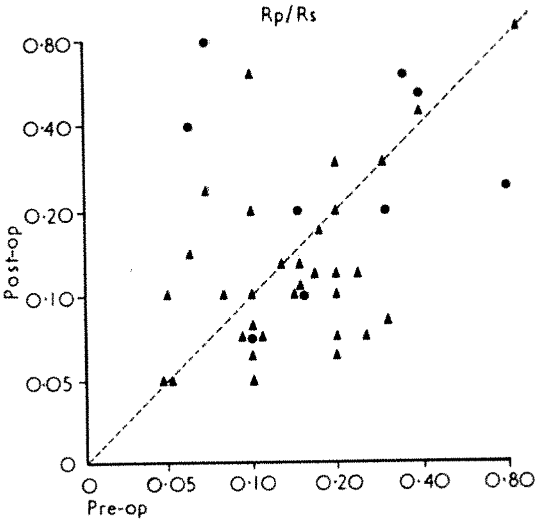

FIG. 7 *The ratio of the pulmonary to systemic vascular resistance (Rp/Rs) was similar before and after Mustard's operation. Solid triangles represent patients who had 'simple' transposition of great arteries and the solid circles those with ventricular septal defects.*

### (e) Peak systolic pressure gradient from left ventricle to pulmonary artery

(i) $P_{LV}$-$P_{PA}$ was significantly smaller postoperatively in all subgroups ($P < 0{\cdot}01$). The greatest change noted was in the subgroup with preoperative ventricular septal defect; the mean gradient preoperatively was 43 mmHg (5·7 kPa), and postoperatively, 17 mmHg (2·3 kPa) ($P < 0{\cdot}01$) (Fig. 6).

(ii) When $P_{LV}$—$P_{PA}$ was related to $\dot{Q}_P/\dot{Q}_S$, there was no significant difference between pre- and postoperative values in the whole group, but the subgroup with preoperative ventricular septal defect tended to have lower gradient/flow indices postoperatively ($P > 0{\cdot}05$) (Table 3). It should be noted that in this subgroup there was a high incidence of postoperative complications (Table 3) which may have influenced some of the values.

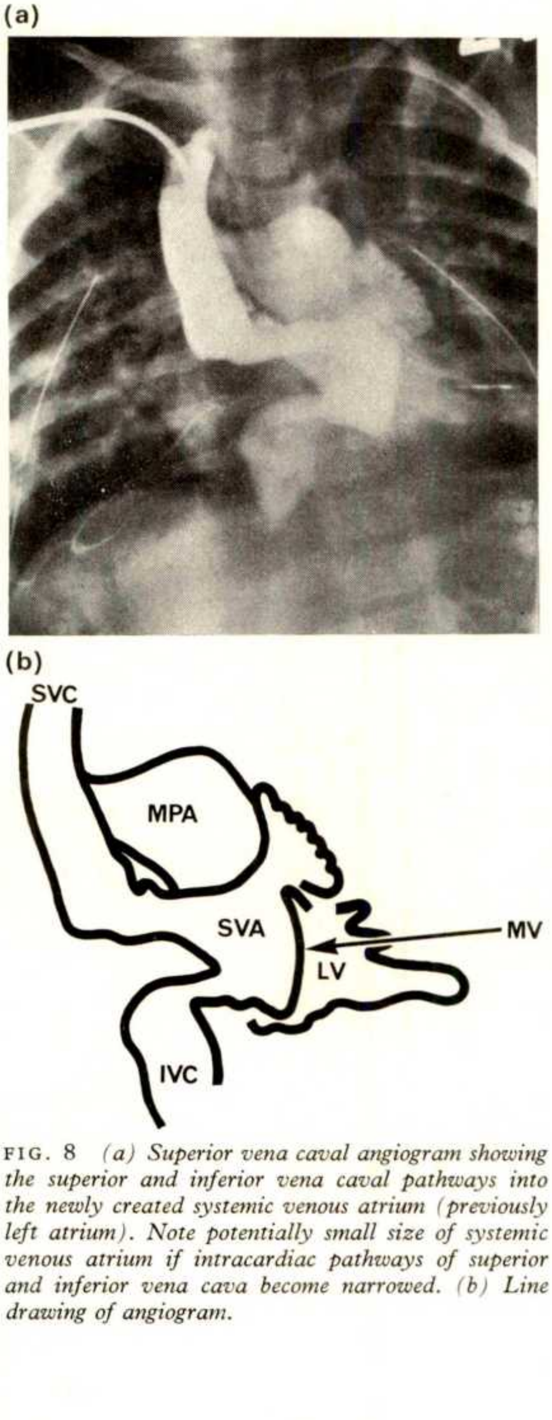

FIG. 8 *(a) Superior vena caval angiogram showing the superior and inferior vena caval pathways into the newly created systemic venous atrium (previously left atrium). Note potentially small size of systemic venous atrium if intracardiac pathways of superior and inferior vena cava become narrowed. (b) Line drawing of angiogram.*

### (f) Rp/Rs

The mean value for $R_p/R_s$ in the whole group was 0·20 both before and after Mustard's operation. There was no significant difference between pre- and postoperative values in any of the subgroups, i.e. preoperative ventricular septal defect, postoperative tricuspid regurgitation, postoperative systemic venous pathway obstruction, and the uncomplicated cases. Some individuals who had preoperative ventricular septal defects and postoperative tricuspid regurgitation showed large changes in either direction (Table 3, Fig. 7).

## Discussion

In Mustard's operation a baffle artificially redivides the atria. Its anatomical position reduces the size of the systemic venous atrium, part of which becomes incorporated into the superior and inferior vena caval pathways. Thus the baffle effectively extends the venae cavae, which in turn enter a relatively small atrial chamber above the mitral valve (Fig. 8). This may explain the characteristic changes in the wave form of the atrial pressure traces. The most striking feature is the steep and rapid descent to the 'y' trough, coinciding with the rapid filling phase of early ventricular diastole, and thus possibly influenced by altered ventricular function. These studies do not indicate any change in left ventricular function, but a rapid 'y' descent is also seen in constrictive pericarditis, and the congestive cardiomyopathies (Wood, 1961) where atrial compliance is also reduced. In cardiac constriction, however, the 'x' and 'y' troughs are usually of similar depth whereas after Mustard's operation the 'x' trough is often barely recognizable. This supports the suggestion that after atrial contraction ('a' wave), the return of venous blood ('v' wave) into a small, relatively non-compliant chamber diminishes the fall of pressure ('x' trough) which usually follows the 'a' wave. The mechanical properties of the systemic venous atrium may also be influenced by the pericardial or 'dacron' baffle itself. Either of these materials may thicken and become relatively rigid, unlike atrial tissues, thereby altering the compliance of the atria. The reduced atrial size and compliance may together account for the observed changes in pressure wave-form.

The systemic venous atrial and superior vena caval pressure tracings described by Venables *et al.* (1974) are similar to those we have found. We agree that the 'y' trough gradient is probably the most sensitive indicator of some obstruction to flow from the venae cavae into the systemic venous atrium. It is conceivable that intracardiac vena caval path-

TABLE 3 *Pre- and postoperative findings in patients with ventricular septal defect*

| Case No. | $\dot{Q}p/\dot{Q}s$ | $P_{LV}$ | | $P_{\overline{PA}}$ | | $Rp/Rs$ | | $P_{LV}—P_{PA}$ | $\frac{P_{LV}—P_{PA}}{(\dot{Q}p/\dot{Q}s)}$ | $P_{LV}—P_{PA}$ | Postoperative complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Pre | Post | Pre | Post | Pre | Post | Pre | Pre | Post | |
| 1 | 1·5 | 100 | 130 | 16 | 70 | 0·07 | 0·80 | 76 | 51 | 10 | TR |
| 2 | 1·0 | 100 | 105 | 36 | 60 | 0·40 | 0·50 | 55 | 55 | 25 | TR |
| 3 | 1·5 | 45 | 35 | 35 | 20 | 0·30 | 0·20 | 0 | 0 | 0 | VSD, TR |
| 4 | 1·0 | 70 | 22 | 14 | 7 | 0·10 | 0·07 | 50 | 50 | 10 | SVO |
| 5 | 1·6 | 100 | 80 | 43 | 50 | 0·35 | 0·60 | 48 | 30 | 20 | VSD |
| 6 | 1·25 | 80 | 45 | 62 | 34 | 0·80 | 0·24 | 0 | 0 | 0 | TR, VSD |
| 7 | 2·6 | 80 | 110 | 15 | 55 | 0·06 | 0·40 | 60 | 23 | 40 | TR, VSD |
| 8 | 1·0 | 24 | 22 | 18 | 12 | 0·15 | 0·10 | 0 | 0 | 4 | SVO |
| 9 | 3·0 | 120 | 60 | 45 | 30 | 0·15 | 0·20 | 62 | 21 | 10 | |
| 10 | 0·6 | 95 | 100 | 11 | 30 | 0·10 | 0·20 | 80 | 133 | 50 | |

$\dot{Q}_P/\dot{Q}_S$ = Pulmonary: systemic flow ratio; $P_{LV}$ = Left ventricular systolic pressure; $R_P/R_S$ = Pulmonary: systemic resistance ratio; $P_{\overline{PA}}$ = Pulmonary arterial mean pressure; $P_{LV}—P_{PA}$ = Systolic pressure gradient between left ventricle and pulmonary artery.

Pre and Post refer to preoperative and postoperative measurements, respectively.

TR, tricuspid regurgitation; VSD, ventricular septal defect; SVO, systemic venous pathway obstruction.

way obstruction exaggerates the smallness of the systemic venous atrium and so contributes to the mechanics of the 'y' trough suggested above. Venables *et al.* (1974) have emphasized that some degree of superior vena caval pathway obstruction may be present in most patients who have had Mustard's operation. Our pressure data from a selected group of patients support this contention, but our clinical and angiographic observations (Stark *et al.*, 1974) suggest that small pressure gradients may be of little importance

The pulmonary venous atrial pressure tracings were somewhat different from the systemic venous atrial pressures. Since the pulmonary veins enter directly into the pulmonary venous atrium, the geometry of which is not altered as radically as the systemic venous atrium, pressure gradients between the pulmonary veins and pulmonary venous atrium were rare. Only two of the patients had pulmonary venous obstruction resulting from contraction of the baffle around the orifices of the pulmonary veins (previously reported by Stark *et al.*, 1972). When tricuspid regurgitation was present, the 'v' wave was dominant and the 'y' trough tended to be lower than the 'x'. However, when there was no tricuspid regurgitation, the 'a' and 'v' waves were of similar height and the 'x' and 'y' troughs of similar depth.

Thus, the pulmonary venous atrial and systemic venous atrial dynamics were not affected in the same way by Mustard's operation. The baffle does not appear to reduce the size of the pulmonary venous atrium because it does not channel the pulmonary venous blood. The normal pressure differential between the pulmonary venous atrium and systemic venous atrium may also be a factor influencing the relative sizes of the atrial chamber after Mustard's operation. The baffle is more likely to encroach upon the systemic venous atrium and vena caval pathways than to reduce the size of the pulmonary venous atrium.

A change of practical significance occurring as a result of Mustard's operation is the reduction in the pressure gradient between the left ventricle and the pulmonary artery. A reduction of pulmonary blood flow after operation may have accounted for the decreased pressure gradient. Some support for this suggestion is found in the similarity of the pre- and postoperative gradient/flow indices which we calculated. However, it must be recognized that the $\dot{Q}_p/\dot{Q}_s$ ratio is not necessarily related to the magnitude of the pulmonary blood flow.

In patients with transposition of the great arteries, pulmonary blood flow values lie within the normal range during the first few days of life and then increase (Keane *et al.*, 1973). This phenomenon may partly explain Tynan's (1972) observation that left ventricular outflow pressure gradients were less than 5 mmHg (0·7 kPa) in the first two weeks of life, but subsequently became larger. He also showed that the pulmonary arterial pressure had decreased, but found no correlation between the pressure gradient and flow ratio. However, Keane *et al.* (1973) published data in graphic form which suggested some relation between the gradient and measured pulmonary blood flow, but which did not reach statistical significance.

It appears that in most cases the magnitude of the left ventricular outflow gradient in transposition of the great arteries is influenced by pulmonary blood flow rather than by a fixed obstruction in the outflow pathway, which frequently occurs at subvalvar leval (Tynan *et al.*, 1969; Silove and Taylor, 1973). The diagnosis of left ventricular outflow tract obstruction requires not only the demonstration of a pressure gradient in the absence of a high flow, but also angiographic confirmation (Silove and Taylor, 1973). This is important because severe fixed stenosis may increase the difficulties of operative management (Breckenridge *et al.*, 1972). Pulmonary vascular disease is an important complication of transposition of the great arteries and frequently presents in infancy (Ferguson *et al.*, 1960: Noonan *et al.*, 1960; Ferencz, 1966; Viles *et al.*, 1969; Newfeld *et al.*, 1974). The influence of Mustard's operation on the pulmonary vascular resistance ($R_p$) is not well understood. Morgan *et al.* (1972) had 3 patients with high postoperative $R_p$ but preoperative values were not available for comparison. Newfeld *et al.* (1974) described 2 patients whose pulmonary vascular disease progressed after Mustard's operation, both on haemodynamic and biopsy evidence. In the present series, we did not have absolute values for pulmonary blood flow and could not calculate pulmonary vascular resistance. Values for $R_p/R_s$ do not necessarily reflect the dynamics of the pulmonary vascular bed. Acknowledging this limitation, the mean value for $R_p/R_s$ both before and after Mustard's operation was 0·20, somewhat higher than might be expected in normal subjects of comparable age. Though the operation does not appear to have significantly influenced average $R_p/R_s$ in the group as a whole, some individuals exhibited large changes in either direction. It was of interest that in 3 of 9 patients whose $R_p/R_s$ values were 0·25 or more preoperatively, the values decreased to below 0·25 after operation. On the other hand, in 3 patients whose preoperative $R_p/R_s$ values were 0·10 or less, the postoperative values rose to 0·40, 0·60, and 0·80, respectively. These 6 patients were equally divided between the subgroups with preoperative ventricular septal defect, postoperative systemic venous pathway obstruction, and tricuspid regurgitation.

A comparison of preoperative and postoperative values for $P_{\overline{PA}}$ did not contribute significantly to the understanding of the pulmonary circulatory changes. $P_{\overline{PA}}$ was more usefully examined in relation to other pressures and flows to derive $R_p/R_s$. However, it appears that the finding of a raised $P_{\overline{PA}}$ postoperatively should lead to investigation for possibly pulmonary venous obstruction or tricuspid regurgitation.

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# Multifocal ventricular parasystolic tachycardia

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*Two cases of spontaneous multifocal ventricular parasystolic rhythm are described. One case showed double and the other fivefold parasystole. All seven foci had an enhanced rate of discharge, ranging from 57 to 102/min and at least three of them showed exit block. Though beats from three foci displayed very short coupling intervals, occasionally interrupting the terminal part of the preceding T wave, in none of the cases was repetitive firing or ventricular fibrillation seen. Both patients had organic heart disease and both are still alive six months after the arrhythmia was first recorded.*

*Problems in the diagnosis of multiple parasystole and some mechanisms which may be responsible for irregular interectopic intervals are discussed. It is concluded that multiple parasystole is probably not a very rare arrhythmia if long strips of simultaneously recorded multiple leads are available.*

Parasystole is characterized by a regular ectopic rhythm coexisting with and independent of the dominant rhythm. The maintenance of regular rhythmicity, despite depolarization of the compartment in which the ectopic focus is situated by the impulses of the dominant rhythm, points to a protective mechanism which is thought to be located within or in the immediate vicinity of the ectopic centre (Schamroth, 1964). These characteristics are manifested electrocardiographically by varying coupling intervals[1] between the beats of the two rhythms and by a simple numerical relation between the interectopic intervals (Katz and Pick, 1956; Chung, 1968; Scherf and Schott, 1973). Fusion beats, if present, support the diagnosis (Scherf and Schott, 1973), but their absence is by no means an argument against it (Marriott, Schwartz, and Bix, 1962). Single ventricular parasystole is not an uncommon arrhythmia. It has been found to occur in 0·08 per cent (1 in 1200) of routine electrocardiograms in a general hospital by Scherf and Schott (1973) and in 0·11 per cent (1 in 900) by Chung, Walsh, and Massie (1964). On the other hand, only very few cases of spontaneous multifocal parasystole are on record (Chung *et al.*, 1964; Chung, 1968; Roelandt, Pool, and Schamroth, 1972; Dolgin, 1973; El-Sherif and Samet, 1975).

It is the purpose of this communication to report and discuss two new cases of multifocal ventricular parasystole.

## Case histories

### Case 1

A 45-year-old woman with hypertensive heart disease complained of palpitation. She was not on digitalis therapy. On physical examination, she had an irregular heart beat and hypertension, and her electrocardiogram and chest *x*-ray film showed evidence of left ventricular hypertrophy. A long continuous rhythm strip (Fig. 1a and b) showed double ventricular parasystole in conjunction with multifocal ventricular extrasystoles.

### Case 2

A 59-year-old man with an old inferior and anterior wall infarction had advanced left and right heart failure. At the time of recording of the electrocardiograms shown in Fig. 2a–e he was on digitalis therapy with a serum digoxin level of 3·0 ng/ml (upper limit of therapeutic range 2·5 ng/ml). Five different ventricular parasystolic rhythms and several ventricular ectopic beats of possible multifocal origin could be identified. One parasystolic rhythm (to be discussed as group 2A) continued for several weeks despite discontinuance of digitalis therapy.

## Analysis of electrocardiograms

Fig. 1 (Case 1) is composed of continuous strips taken from a long, simultaneous recording of leads

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[1] The independent character of continuous parasystolic rhythm precludes true coupling to the beats of the dominant rhythm. Thus, in most cases of parasystole, this term is a misnomer. Its use in this context will only be continued because of its convenience.

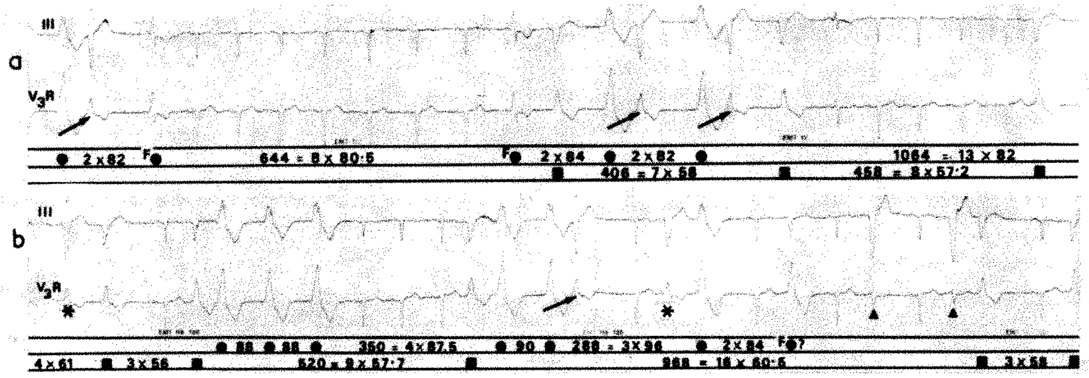
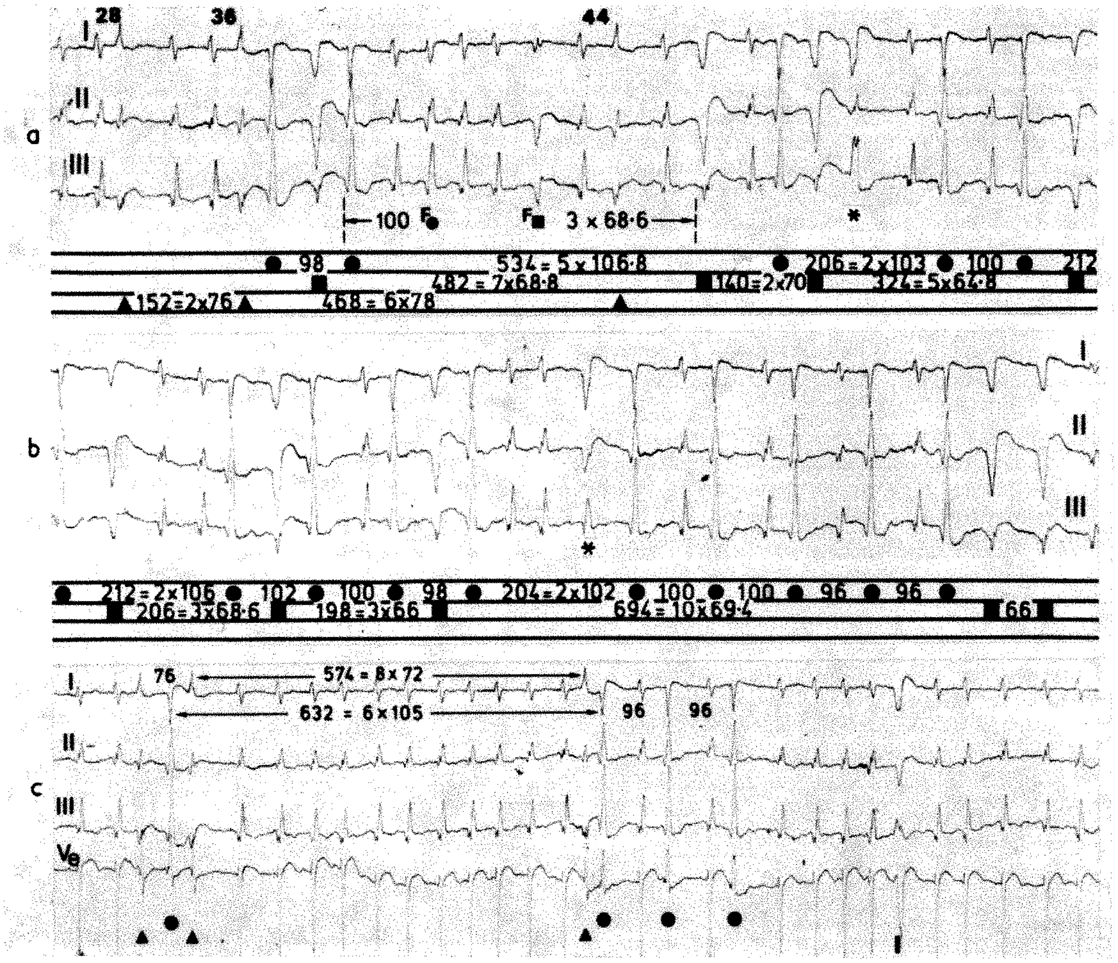


FIG. 1 *Case 1. Continuous strips (a and b) taken from a simultaneous recording of leads III and V3R. Parasystolic beats of group A and B are indicated by closed circles and squares, respectively. Ectopic beats marked with asterisks, arrows, and triangles show different but constant coupling intervals. Note that those marked with arrows only follow the parasystolic beats of group A (closed circles). F=fusion beat. F?=possible fusion beat. See text for further discussion.*



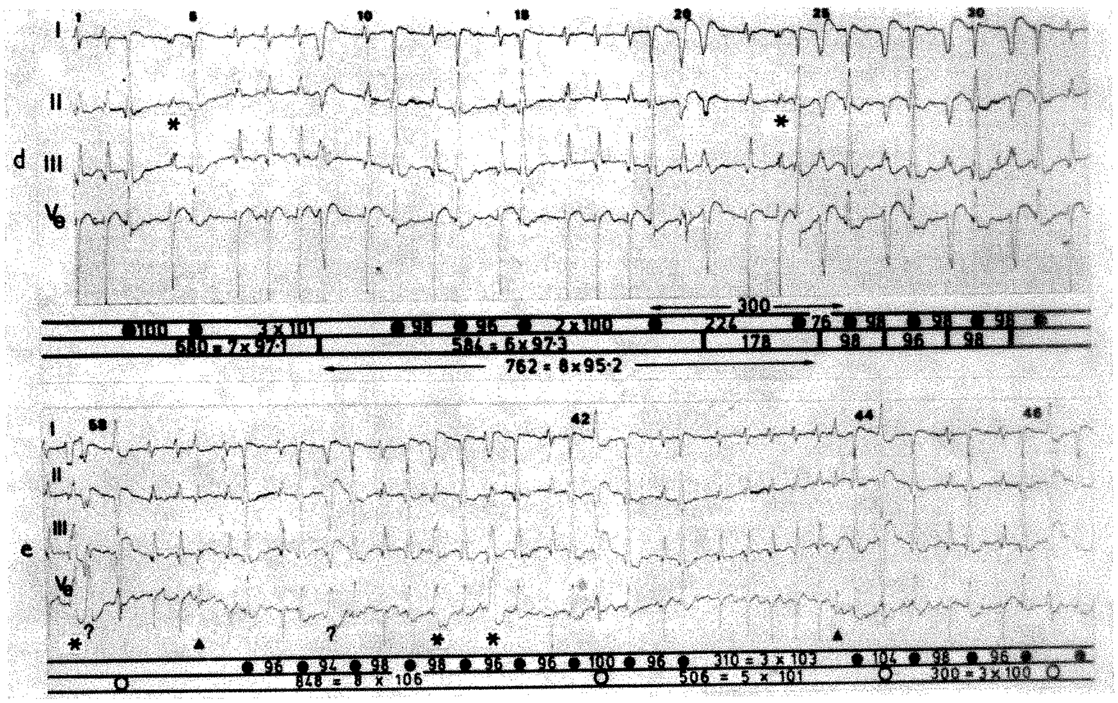


FIG. 2 *Case 2. Representative strips taken from a simultaneous recording of leads I, II, III, and ensiform lead. (a) Three different parasystolic rhythms are indicated by closed circles (group A), squares (group B), and triangles (group C). Numbers in the upper part of the figure indicate coupling intervals of beats of group C (triangles): note the extremely short coupling interval of the first beat of this group. Numbers in the lower part of the electrocardiogram indicate interectopic intervals measured from supposed fusion beats (F) to the interrupted vertical lines, each of which indicates the onset of a pure parasystolic beat. The asterisk marks an ectopic beat of undetermined origin. (b) Continuous with Fig. 2a. The parasystolic cycle length of group B (squares) appears at the end of the figure. Group A parasystolic rhythm (closed circles) displays an exit block at the end of the strip. The ectopic beat marked with an asterisk is of undetermined origin. (c) This strip is continuous with Fig. 2d but not with 2b. The ectopic beat marked with a vertical bar belongs to group D. Numbers in the upper part of the record indicate interectopic intervals. Note the shortest manifest interval of Group C (triangles) in the left-hand part of the figure (compare with Fig. 2a). (d) Continuous with Fig. 2c, but not with 2e. Beats are numbered in the upper part of the record. Note the constant QRS configuration and varying coupling intervals of the ectopic beats which have been marked with an asterisk. Only two of these ectopic beats were recorded in the whole strip. Also note the short episode of bi-directional parasystolic tachycardia with fixed coupling between groups A and D at the end of the strip. See text for further discussion. (e) Representative strip taken from the same record as Fig. 2a–d. Beats arising from the fifth parasystolic centre (group E) are indicated by open circles. In this strip the asterisks indicate ectopic beats with fixed coupling. Other symbols as in Fig. 2a–d. Numbers in the upper part of the record indicate coupling interval of group E beats.*

III and V3R. The record shows sinus rhythm interrupted by multiform ventricular ectopic beats. Those marked with arrows, asterisks, and triangles, show fixed but different coupling intervals. They probably represent ventricular extrasystoles of multifocal origin. Two groups of ectopic beats have distinct and constant QRS patterns and both show variable coupling intervals. They are indicated by closed circles and squares in the diagrams and are discussed as group 1A and 1B, respectively.

*Group 1A* beats are readily identified by the tall R waves in V3R and the notched R waves in lead III. Their coupling intervals vary from 48 to 108[1]. On several occasions the ectopic cycle length (Scherf and Schott, 1973) is directly measurable (Fig. 1b) and constant at 88 to 90, corresponding to a rate of 66·6 to 68/min. Longer interectopic intervals are near multiples of the ectopic cycle length, but the variation in the calculated intervals (from 80 to 96) is large. The ectopic intervals, however, seem to lengthen slightly from Fig. 1a to 1b, corresponding to a slight decrease in rate. Such slowing of the ectopic centre might, in this case, afford a possible explanation for the fact that the interval of 288 (Fig. 1b) is slightly longer than three times the cycle length, which is in contrast to the usual observation in parasystole (Chung, 1968; Scherf and Schott, 1973). Alternatively, lengthening of a parasystolic interval could also be the result of one or more of the following: changes in impulse formation or conduction resulting from concealed re-entry (Singer *et al.*, 1974), concealed conduction of a preceding blocked impulse in the ectopic-ventricular junction, or relative refractoriness of the myocardium following a preceding depolarization (Vedoya, quoted by Scherf and Schott, 1973).

In support of the parasystolic character of the rhythm is the finding of fusion beats, marked with an F in the diagram. The true nature of the nineteenth QRS complex (F?) in Fig. 1b could not be established with certainty. It may represent a fusion beat between group 1A and group 1B, or between group 1A or 1B and one of the extrasystolic beats, or it may represent the activity of another ectopic centre.

The ectopic beats of *group 1B* are characterized by R waves in V3R and QS deflections in lead III. Their coupling intervals vary from 52 to 92 and their interectopic intervals are multiples of 56 to 61 (mean 58·8) corresponding to a rate of about 102/min.

In group 1A and in group 1B an exit block must be postulated to account for the occasional absence of these beats outside the ventricular refractory period (Scherf and Bornemann, 1961; Pick, 1966; Pick, Langendorf, and Jedlicka, 1973).

Fig. 2a–e is composed of representative strips taken from a long simultaneous recording of leads I, II, III, and the ensiform lead (Ve) of Case 2. The basic rhythm is atrial fibrillation with a fast ventricular response. The conducted supraventricular beats have a notched QR complex in leads II and III, consistent with old inferior wall infarction. In all the strips several multiform ventricular ectopic beats can be identified, five groups of which show a remarkably constant QRS configuration in all the represented leads, irrespective of their widely varying coupling intervals. These are discussed below as groups 2A, B, C, D, and E. Furthermore, it is to be noted that the supraventricular beats do not differ significantly in QRS configuration, even when their degree of prematurity and length of the preceding RR interval are comparable to those of beats of groups A–E. Thus, aberrancy as the cause of the abnormal QRS configurations of groups A–E can almost certainly be excluded (Marriott and Sandler, 1966; Singer and Ten Eick, 1971).

Ectopic beats of *group 2A* are indicated by closed circles in the diagrams. Their QRS complex is characterized by an rS′ deflection in lead I and a QR in leads II and III. They represent the most frequently occurring ectopic beats and have coupling intervals ranging from 24 (e.g. second group 2A beat in Fig. 2c) to 58. Short manifest intervals range from 94 to 104, though the majority are remarkably constant at 96 to 100, denoting a rate of 60 to 62/min. Longer interectopic intervals are multiples of 101 to 107. Furthermore, the eleventh QRS complex in Fig. 2a is a fusion beat with a conducted supraventricular impulse. From these observations there seems to be no doubt that group 2A represents the enhanced activity of a parasystolic centre.

The intervals of 224 and 76 which follow each other in Fig. 2d are of interest, since they differ from the presumed ectopic cycle length. However, their sum equals 300, or 3 × 100. Two explanations seem possible. The first one invokes regular firing at the presumed cycle length of 100 with delayed conduction during the exit of impulse 24 in Fig. 2d. This causes a corresponding shortening of the subsequent interval. This explanation seems very likely, since beat 24 occurs during the relative refractory phase at the end of the preceding T wave. A similar mechanism has been advanced by Vedoya (quoted by Scherf and Schott, 1973) to explain interectopic intervals which are slightly longer than a whole number multiple of the ectopic cycle length. Delayed conduction during the exit of the impulse has also been shown during fixed rate artificial pacing (Scherf, 1970; Pick *et al.*, 1973). The second explanation assumes sudden dissipation of an exit block (Scherf and Bornemann, 1961), pointing to a smaller common denominator of about 25. Thus the actual discharge rate would be approximately 240/min. It should be pointed out, however, that even if we assume the slower discharge rate of about 60/min, an exit block (Pick, 1966; Pick *et al.*, 1973) must occasionally be postulated, e.g. at the end of the strip in Fig. 2b.

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[1] All intervals are expressed in hundredths of a second, unless otherwise specified.

*Group 2B* beats are characterized by broad QS deflections in leads I, II, and III. They are represented by squares (Fig. 2a and b) and have coupling intervals of 50 to 64. The ectopic cycle length (end of Fig. 2b) is 66, corresponding to a discharge rate of 91/min. Longer intervals, which in this case can adequately be explained by ventricular refractoriness during the Q-aU interval (Pick, 1953; Watanabe, 1971), are multiples of 65 to 70. The fourteenth QRS complex (F) in Fig. 2a is a fusion beat between a group 2B and a conducted supraventricular impulse.

The most conspicuous morphological features of *group 2C* beats are the narrow peaked R wave in lead I and the notched, relatively small QS deflection in lead III. The ectopic beats of this group are represented by triangles in Fig. 2a and 2c. Coupling intervals vary from 28 to 44. The shortest manifest interval (Fig. 2c) is 76. Longer intervals are multiples of 72 to 78, mean 74·7, corresponding to a rate of about 80/min. Only few, occasionally isolated, beats of group 2C were recorded. The possibility should, therefore, be considered that group 2C might represent ventricular extrasystoles with a conduction disturbance during their exit (Langendorf and Pick, 1955). However, the finding that longer interectopic intervals in the presence of an irregular dominant rhythm are an approximate multiple of the short one, favours a parasystolic mechanism. The occurrence of only few beats of group 2C must then either be the result of the combination of ventricular refractoriness and an increase in exit block, or of temporary loss of automatic activity (Schamroth and Marriott, 1961).

*Group 2D* beats are indicated by vertical bars (Fig. 2d) and characterized by broad QS deflections in leads I and II and, unlike group 2B, a notched R in lead III. Coupling intervals vary from 32 to 64. Short manifest intervals are constant at 96 to 98 (rate 61/min) and the long interval between beats 9 and 21 (Fig. 2d) is a multiple of 97. The subsequent interval of 178, however, is not: the two explanations which have been suggested above for group 2A to account for the intervals between beats 19 to 24 and 24 to 26 (Fig. 2d) are again possible; a third possibility, namely intermittent parasystole caused by temporary loss of protection (Schamroth and Marriott, 1961; Steffens, 1971; Watanabe, 1971; Cohen, Langendorf, and Pick, 1973; Kinoshita, 1974) and depolarization by beat 22, seems unlikely in view of the fact that the preceding longer interectopic interval was not disturbed and remained a simple multiple of the presumed ectopic cycle length. A short episode of bidirectional ventricular parasystolic tachycardia results from the activity of groups 2A and D at the end of Fig. 2d. There is also a short episode of fixed coupling between the two rhythms in the same part of the record, caused by the equal rates of these two parasystolic rhythms (Langendorf and Pick, 1967).

Finally, the ectopic beats of *group 2E* show tall R waves in lead I and QS deflections in leads II and III. Isolated beats were recorded on several occasions. Four of them are seen in Fig. 2e and marked with open circles. Coupling intervals range from 42 to 58 and the interectopic intervals are multiples of 100 to 106, corresponding to a rate of 57 to 60/min. As in group 2C, ventricular refractoriness and exit block or temporary dissipation of automatic activity must be postulated to account for the brevity of this episode of manifest group 2E parasystolic activity.

## Discussion

Several authors have focused attention on electrophysiological mechanisms which may be responsible for sudden and at times rather wide variations in the manifest or calculated shortest interectopic intervals in parasystole (Schamroth and Marriott, 1961; Scherf and Bornemann, 1961; Steffens, 1971; Cohen *et al.*, 1973; Scherf and Schott, 1973; Kinoshita, 1974; Singer *et al.*, 1974). In such cases, the diagnosis of parasystole must be based on the demonstration of variable coupling and constant interectopic intervals during at least one, but preferably several episodes of the ectopic rhythm. But even then, there is controversy concerning the acceptable variability in what are to be considered constant interectopic intervals. It has been pointed out that, when longer rhythm strips are analysed, some degree of irregularity is almost invariably present (Chung, 1968; El-Sherif and Samet, 1975). It is also evident that when interectopic intervals are measured to or from a fusion beat, they may differ from those measured between two pure ectopic beats, since with a fusion beat one sometimes does not know exactly at what moment the ectopic depolarization starts to contribute to the morphology of the mixed beat.

With these considerations in mind, we feel that in Case 1 double, and in Case 2 quintuple ventricular parasystole can be diagnosed. During the analysis of the electrocardiogram of Case 2 we have already indicated that aberrancy of supraventricular impulses can be excluded because of the constant QRS configuration of each group in multiple leads, irrespective of their degree of prematurity and length of the preceding RR interval (Marriott and Sandler, 1966; Singer and Ten Eick, 1971). For the same reasons variable intraventricular conduction during a single ectopic ventricular tachycardia with an irregular discharge and varying degrees of exit block can be excluded.

Our cases show that the diagnosis of multifocal parasystole is greatly facilitated and can sometimes only be established when long, multiple, and simultaneously recorded leads are available. In a single lead, complexes arising from different parasystolic foci may display near-identical configurations, e.g. Case 2, lead I, QRS configuration of groups B and D. Furthermore, when such complexes are interspersed in a single lead, the apparent irregularity of interectopic intervals may even lead to rejection of the diagnosis of parasystole.

With the availability of multiple simultaneously recorded leads multifocal parasystole may well turn out not to be as rare an arrhythmia as would be inferred from the rarity of published reports. From an electrophysiological point of view one would also expect that the primary derangement which leads to regular impulse formation within and protection around an ectopic focus, will exert the same type of influence on other groups of pacemaking cells in the atria or ventricles; though the sensitivity of these cells to a particular environmental change may differ (Hoffman and Cranefield, 1964), identical cell types, such as Purkinje fibres, may be expected to react in the same way.

It is also interesting to find that in our cases all the seven parasystolic centres had an enhanced rate of discharge, ranging from 57 to 102/min. In three of these an exit block could be shown. Also unusual is the observation that beats arising from three of the ectopic centres (Case 2, groups A, C, and D) at times had extremely short coupling intervals, leading to interruption of the terminal part of the T wave of the preceding beat. In none of these cases was repetitive firing or ventricular fibrillation seen.

As in all other published cases (Chung *et al.*, 1964; Chung, 1968; Roelandt *et al.*, 1962; Dolgin, 1973; El-Sherif and Samet, 1975), our patients had organic heart disease. They are, however, still alive six and nine months after the arrhythmia was first detected.

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# Ventricular arrhythmias in syndrome of balloon deformity of mitral valve
## *Definition of possible high risk group*

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*Twenty patients clinically identified as having balloon deformity of the mitral valve were studied to assess the incidence of ventricular arrhythmias. Echocardiography and phonocardiography were used to confirm the nature of the mitral valve lesion. Continuous 24-hour electrocardiograms were obtained from all patients and analysed by a computer and 2 observers. One patient had ventricular fibrillation and 3 patients had ventricular tachycardia. There was a high incidence of other less severe forms of ventricular arrhythmias. Eight patients had inferolateral ST and T wave abnormality on the resting electrocardiogram, and were described as having the auscultatory-electrocardiographic variant of the balloon mitral valve syndrome. The occurrence of serious ventricular arrhythmias (ventricular fibrillation and tachycardia) was significantly more frequent in this group. This raises the possibility that the resting electrocardiogram may identify those patients with balloon deformity of the mitral valve who are at risk from sudden death.*

Balloon deformity of the mitral valve has been detected with increasing frequency since the characteristic mid-systolic click was first described by Cuffer and Barbillon (1887). In most patients the balloon deformity has little haemodynamic consequence but the condition has been associated with ventricular and supraventricular arrhythmias (Hancock and Cohn, 1966; Kreisman *et al.*, 1971; Gooch *et al.*, 1972; Sloman, Wong, and Walker, 1972; Jeresaty, 1973; Rizzon *et al.*, 1973; DeMaria *et al.*, 1974; Gulotta *et al.*, 1974; Schaal, Fontana, and Wooley, 1974; Winkle *et al.*, 1975), and sudden death has been reported in 9 patients (Hancock and Cohn, 1966; Barlow *et al.*, 1968; Trent *et al.*, 1970; Jeresaty, 1973; Marshall and Schappell, 1974; Rakowski *et al.*, 1975). The incidence of the lesion is not known accurately but in a recent necropsy series the abnormality was detected in 0·33 per cent of the population studied (Rizzon *et al.*, 1973), and clinical reports have suggested incidences from 6 to 10 per cent (Markiewicz *et al.*, 1975; Brown, Kloster, and DeMots, 1975; Procacci *et al.*, 1975). Reports of the condition are confused by the heterogeneity of pathologies which can cause mechanical dysfunction of the mitral valve leaflets. The incidence of arrhythmias may vary in each group and it is possible that sudden arrhythmic death is more common in a specific population.

The object of the current study was to assess the type and significance of rhythm disorders in patients with idiopathic balloon deformity of the mitral valve.

## Patients and methods

### Clinical investigation

The subjects were 20 patients attending the department of cardiology in the Royal Infirmary and Royal Hospital for Sick Children of Edinburgh who had the clinical features of balloon deformity of the mitral valve without coexisting cardiovascular disease. There were 13 female and 7 male patients whose ages ranged from 12 to 61 years. Initially the diagnosis was made on the presence of a mid-systolic click or late systolic murmur or both. The

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patients were examined by 12-lead electrocardiography, phonocardiography, posteroanterior chest *x*-ray film, echocardiography, and 24-hour continuous ambulatory electrocardiographic monitoring. The latter recordings were obtained using the Oxford Instruments Miniature Analogue Tape Recording System which allowed all patients to undertake all normal activities without restriction. The electrocardiographic lead used was a modified V5.

### 24-hour electrocardiographic analysis

The tape recordings were replayed at 60 times real speed and processed by a Neilson Arrhythmia Computer (Neilson, 1974) programmed to detect ventricular ectopic beats. This produced a chart of the 24-hour ventricular ectopic beat activity. The computer also 'froze' arrhythmias in a solid-state memory from which they could be written out in real time on standard electrocardiographic paper. During the processing, the recordings were observed by two independent observers who scored arrhythmias and ensured accuracy of the computer programme if background noise levels or electrical axis shift necessitated modification. The tape recordings were repeated if because of poor quality less than 22 out of 24 hours were capable of analysis. No attempt was made to analyse the recordings of atrial ectopic beat activity but the system identified supraventricular tachycardia.

### Arrhythmia definitions

Ventricular tachycardia was defined as 3 or more consecutive ventricular ectopic beats at a rate greater than 100/min. R-on-T phenomenon was defined as a ventricular ectopic beat falling within 85 per cent of the prevailing QT interval. Coupled ventricular ectopic beats were those occurring in pairs with R-R less than 400 ms. Ventricular ectopic beats were defined as frequent when they occurred more often than 30 an hour.

### Auscultatory-electrocardiographic variant

Routine 12-lead electrocardiograms were carefully examined for inferolateral ST and T wave abnormalities and a group of patients with these changes was described as the auscultatory-electrocardiographic variant of the balloon deformity of the mitral valve (Humphries and McKusick, 1962; Barlow and Bosman, 1966; Sloman *et al.*, 1969; Liedtke *et al.*, 1973; Pocock and Barlow, 1970; Ehlers *et al.*, 1970; Stannard *et al.*, 1967).

## Results

### Clinical presentation

Of the 6 patients who were asymptomatic, 5 had been referred because auscultatory abnormalities had been found on routine examination; in one patient, ventricular ectopic beats were noted on an electrocardiogram. Of the remaining 14 patients, 12 had complained of symptoms suggestive of an arrhythmia, namely syncope, palpitation, or dizziness; 7 of the 14 also complained of ill-defined chest pain. The recorded duration of symptoms or signs ranged from a few days to 30 years.

### Routine electrocardiogram

In 9 of the 20 patients, the routine 12-lead electrocardiogram was normal. In 3, varying degrees of right bundle-branch block were present. In the remaining 8, non-specific ST and T wave changes were present in the inferolateral leads; these patients constituted the group already defined as the auscultatory-electrocardiographic variant of the balloon deformity of the mitral valve. There was no apparent difference in age or sex distribution in this group compared with the other patients, but complaints of lassitude, breathlessness, and chest pain were more common.

### Posteroanterior chest *x*-ray film

Of the 20 patients, 8 showed minimal cardiomegaly on a routine chest *x*-ray film (cardiothoracic ratio $>50\%$).

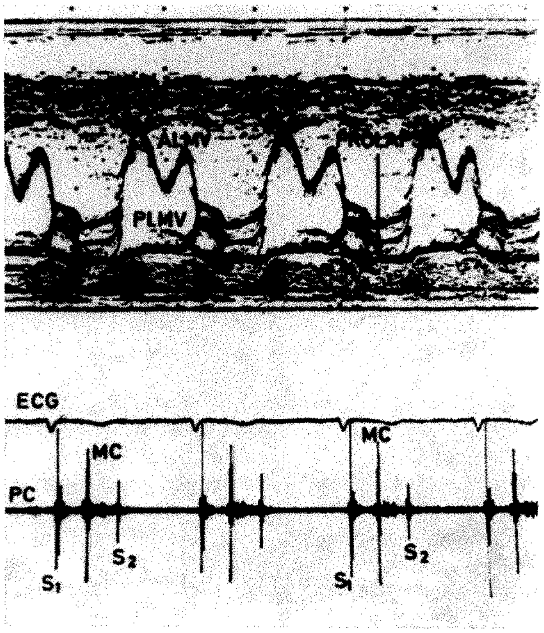

FIG. 1 *Typical echocardiogram and simultaneous phonocardiogram.*

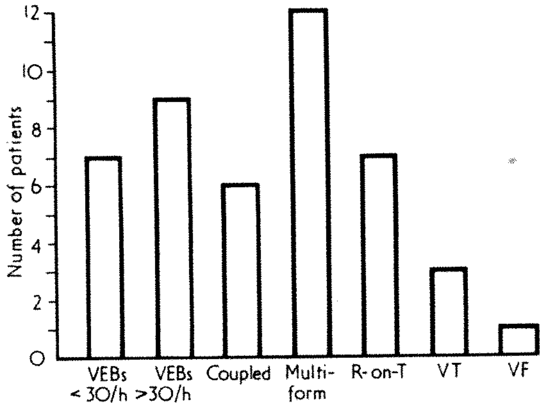

FIG. 2 *Numbers of patients (total 16) showing each type of ventricular arrhythmia on 24-hour continuous electrocardiogram.*

### Phonocardiography

The combined features of a mid-systolic click and late systolic murmur were confirmed in 18 of 19 patients. The phonocardiogram was repeatedly unsatisfactory in one patient; another had only a late systolic murmur: echocardiography confirmed mitral valve prolapse in both patients. Several attempts were required with some patients before a satisfactory record was obtained.

### Echocardiography

This showed prolapse of one or both mitral valve leaflets in 17 patients. In 3 patients the mitral echogram was normal, but a midsystolic click and late systolic murmur were confirmed by phonocardiography. Fig. 1 shows a typical tracing with the simultaneous phonocardiogram.

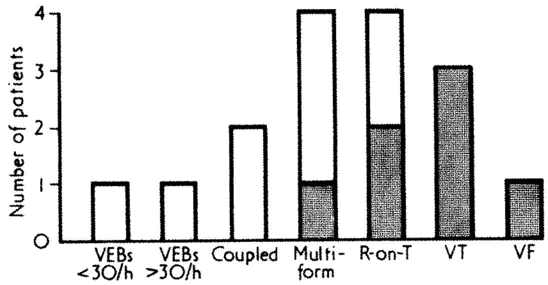

FIG. 3 *'Most severe' ventricular arrhythmia shown in 16 patients on 24-hour continuous electrocardiogram. The 'severity' of arrhythmia has been arbitrarily graded from infrequent VEBs to VF. Shaded areas represent patients with the auscultatory-electrocardiographic variant.*

### Ambulatory electrocardiographic monitoring

Only one patient had no arrhythmia recorded during the 24 hours. Supraventricular arrhythmias alone were found in 3 patients, which in 2 were at a rate of 160/min while the third, a girl of 12, developed atrial flutter with 1:1 atrioventricular conduction and a ventricular rate of 300/min.

The remaining 16 patients all showed ventricular arrhythmias of varying type. Fig. 2 shows the numbers of patients with specific arrhythmias on the 24-hour recording. Multiform ventricular ectopic beats were the most common form of ventricular arrhythmia. We have not attempted to document the numbers of episodes of each arrhythmia in each patient as on repeated recordings these figures were variable. Fig. 3 shows the results when the ventricular arrhythmias are arbitrarily graded in 'severity' from infrequent ventricular ectopic beats to ventricular fibrillation. Each patient is classified on the basis of the most 'severe' arrhythmia detected on their 24-hour electrocardiogram. Ventricular fibrillation was detected in one patient. Her tape recorder had been equipped with an alarm device which, when pressed, produced a pulse on a parallel tape track. The tracing of this event is shown in Fig. 4. This arrhythmia produced syncope but fortunately was self-terminating. Three patients showed ventricular tachycardia and in 4 the R-on-T phenomenon was the most 'severe' arrhythmia detected.

### Relation between ventricular arrhythmias and resting 12-lead electrocardiogram

In Fig. 3 the hatched areas represent those patients with the auscultatory-electrocardiographic variant of the balloon mitral valve as previously defined. Thus ventricular fibrillation and ventricular tachycardia were seen only in patients with this abnormality on their electrocardiogram. This difference is statistically significant ($P < 0{\cdot}05$) ($\chi^2$ + Yates correction). This accounts for 4 of the 8 patients of this group. Two others had R-on-T phenomenon, one had multiform ventricular ectopic beats, and the remaining patient had only a supraventricular tachycardia at a rate of 160/min. The high incidence of 'serious' ventricular arrhythmias in those patients having inferolateral ST and T wave changes on the resting electrocardiogram suggests an association between these observations.

## Discussion

Continuous 24-hour electrocardiographic monitoring of 20 patients with the clinical features of apparent idiopathic balloon deformity of the mitral

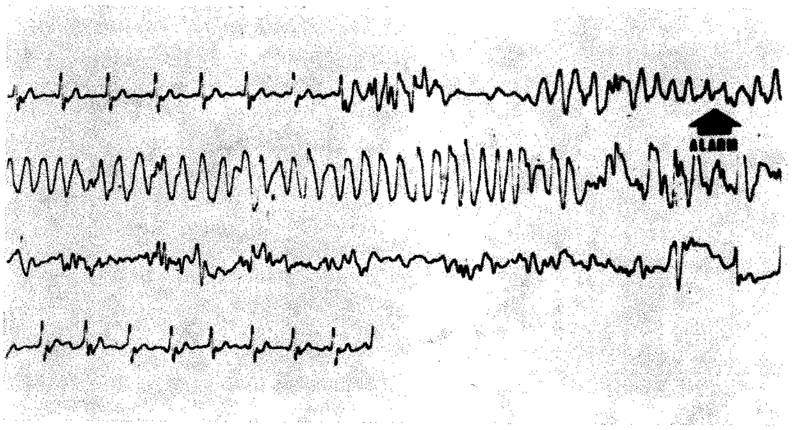

FIG. 4 *Ventricular fibrillation detected in one patient. Patient pressed the alarm button as shown.*

valve has shown that the incidence of arrhythmias, and in particular of 'serious' forms of ventricular arrhythmia, may be higher than has been widely recognized in the past. The coexistence of rhythm disorders and mechanical dysfunction of the mitral valve in the condition has been attributed to a myocardial disorder (Scampardonis *et al.*, 1973; Gulotta *et al.*, 1974) possibly secondary to an initially abnormal mitral valve apparatus (Nutter *et al.*, 1975). Whether or not the non-specific ST and T wave changes are taken as evidence of a disorder in the myocardium, it is possible that they may identify a group of patients who are at high risk from arrhythmias. In support of this suggestion are the 11 reported patients with balloon deformity of the mitral valve who died suddenly or had ventricular fibrillation, and for whom electrocardiographic data are available: 8 had the auscultatory-electrocardiographic variant of the syndrome and 3 showed QT prolongation (Hancock and Cohn, 1966; Barlow *et al.*, 1968; Trent *et al.*, 1970; Jeresaty, 1973; Marshall and Shappell, 1974; Rakowski *et al.*, 1975).

These results and the previous reports of sudden death suggest that it is important to diagnose this condition. Unfortunately the recognition of the syndrome is made difficult by the variability of symptoms and signs. Often the presenting complaints of vague chest pain, lassitude, and light-headedness suggest a functional diagnosis. The auscultatory features of a midsystolic click or late systolic murmur or both may not be constantly present in an individual and it is often difficult to obtain an echocardiographic record of the posterior leaflet of the mitral valve. Left ventricular cine-angiography carries a small but definite risk. For these reasons the auscultatory signs remain the simplest and most useful diagnostic feature. The expense and personnel involved in long-term ambulatory monitoring prohibit its use in an undefined population, but our results suggest that it is possible that the 12-lead electrocardiogram can define a 'high risk' group for whom this technique could be of value.

Allen, Harris, and Leatham (1974) report a good prognosis for the condition of balloon deformity of the mitral valve but their exclusion of patients with electrocardiographic abnormalities may have biased the results in favour of those less likely to develop arrhythmias. In contrast, our experience confirms that ventricular arrhythmias are a part of the syndrome of balloon deformity of the mitral valve and suggests that all patients with an abnormal resting electrocardiogram by virtue of inferolateral ST and T wave changes should be investigated by long-term ambulatory monitoring even in the absence of symptoms. In the 20 patients studied all episodes of ventricular tachycardia and fibrillation were seen in individuals with such electrocardiographic abnormalities. It is not yet known whether ventricular arrhythmias associated with balloon deformity of the mitral valve are well tolerated or if they carry the long-term risk of sudden death. At present it is our policy to treat those patients who are symptomatic because of their arrhythmias and those in whom we have detected ventricular tachycardia or fibrillation. The choice of antiarrhythmic agent requires care as it is likely that long-term medication will be necessary. Some patients will respond to beta-adrenergic blocking drugs but others are resistant (Gooch *et al.*, 1972), and in this situation, the orally active antiarrhythmic drug, mexiletine (Talbot *et al.*, 1973; Campbell *et al.*, 1973, 1975) given three times daily has been well tolerated and effective in abolishing ventricular tachycardia and fibrillation in our 4 patients with these rhythm disorders. Ambulatory electrocardiographic monitoring has proved useful in evaluating the effect of therapeutic intervention and has allowed us to use the minimal drug dosage consistent with arrhtyhmia control. It is clearly important to establish whether long-term anti-arrhythmic therapy in these patients can reduce the risk of sudden arrhythmic death.

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# Ventriculo-atrial conduction time during reciprocating tachycardia with intermittent bundle-branch block in Wolff-Parkinson-White syndrome[1]

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*Records from patients with the Wolff-Parkinson-White syndrome were reviewed with particular emphasis on the occurrence of bundle-branch block aberration during reciprocating tachycardia and the significance of this observation with respect to accessory pathway location. Increase by greater than 25 ms in the ventriculo-atrial interval during reciprocating tachycardia with bundle-branch block, when compared to reciprocating tachycardia with normal intraventricular conduction, occurred only with right or left free wall accessory pathways. No patient with a septal accessory pathway proven by epicardial mapping showed a ventriculo-atrial interval prolongation greater than 20 ms during bundle-branch block aberration. Measurement of ventriculo-atrial interval during bundle-branch block aberration also helped to diagnose accessory pathways with unidirectional retrograde conduction. Measurement of cycle length changes alone with failure to measure AH and HV intervals as well as ventriculo-atrial times, may give misleading information. In one patient increase in cycle length during left bundle-branch block was the result of prolonged HV interval rather than prolonged ventriculo-atrial interval. In another patient cycle length remained the same during bundle-branch block while the ventriculo-atrial interval increased by an increment identical to the decrease in AH interval.*

Techniques have recently been developed for epicardial mapping of ventricular excitation (Durrer and Roos, 1967) and for surgical division of accessory pathways (Sealy *et al.,* 1974) in patients with the Wolff-Parkinson-White syndrome. Application of these techniques demands precise localization of accessory pathways before operation. Bundle-branch block occurs in supraventricular tachycardia of any mechanism when the relative refractory period of either bundle-branch system is encountered (Damato and Lau, 1970). When associated with the Wolff-Parkinson-White syndrome, increase of the cycle length during reciprocating tachycardia associated with bundle-branch block has been reported to implicate participation of an accessory pathway in the ventricle showing the bundle-branch block (Motté *et al.,* 1973; Coumel and Attuel, 1974). In this communication we make some additional observations about this phenomenon and stress the need to measure ventriculo-atrial conduction time correctly to interpret cycle length changes. This has been commented on previously (Neuss, Schlepper, and Thormann, 1975).

## Methods

Between January 1968 and January 1976, 125 patients with the Wolff-Parkinson-White syndrome were studied in the Clinical Electrophysiology Laboratory of the Duke University Medical Center. Records from these patients are the source of this study. All patients gave informed consent for these studies. Antiarrhythmic therapy was discontinued 48 hours before the first day of study and all electrophysiological phenomena described in this report were recorded before the administration of any antiarrhythmic treatment during the study. Four catheters were positioned for intracardiac recording and stimulation. A 6F tripolar catheter was

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introduced percutaneously from the right femoral vein and positioned across the tricuspid valve for recording the His bundle electrogram as described by Schlerlag *et al.* (1969). A 6F quadripolar or hexapolar catheter was introduced from a left antecubital vein into the coronary sinus for recording left atrial and posterobasilar left ventricular electrograms. Recording and stimulation of the right atrium and right ventricle were done by two 6F quadripolar catheters introduced from the right antecubital vein and right femoral vein, respectively. Heparin 100 units per kg bodyweight was administered after introduction of these catheters.

Intracavitary electrograms were obtained by filtering out frequencies below 50 Hz and above 1 kHz. Simultaneous recordings of these electrograms and surface electrocardiogram lead V1 were recorded on magnetic tape at a speed of 9·5 cm/s. Refractory periods were determined and arrhythmias were induced using a stimulator[1] using photoelectric isolation which delivered programmed impulses of 2 ms duration of twice diastolic threshold. The tapes were played back on a Mingograf 800 8 channel ink jet recorder at paper speeds of 100 mm/s or 200 mm/s.

Fifty-one of these patients have subsequently undergone thoracotomy with epicardial mapping (Durrer and Roos, 1967) being performed before attempted surgical division of the accessory pathway (Sealy *et al.*, 1974). The operative data enabled classification of the accessory pathway location as left ventricular free wall, right ventricular free wall, septal, or multiple locations. All patients with multiple pathways and all patients who showed only one QRS configuration during electrophysiological study were excluded. One patient was excluded because of coexistence of Kent and Mahaim tracts (Tonkin *et al.*, 1975a). In the remaining 23 patients, the following measurements were made during reciprocating tachycardia with both normal intraventricular conduction and bundle-branch block (in two patients, reciprocating tachycardia did not occur but measurements could be made on single atrial echo beats). Measurements were made during one paroxysm of reciprocating tachycardia to avoid slight changes in cycle length, which may occur between paroxysms.

## Definition of terms

### AH interval

This interval is from the rapid component of the bipolar medial right atrial electrogram to the onset of the His bundle deflection, both electrograms being recorded by the catheter positioned across the tricuspid valve.

### HV interval

This interval is from the onset of the His bundle deflection to the earliest recording of ventricular activation, either on a surface electrocardiogram lead or intracardiac electrogram.

### VA interval

This interval is from the earliest recording of ventricular activation to the rapid component of the bipolar atrial electrogram, whenever possible this being recorded from the site closest to the accessory pathway.

## Results

Details of the 18 patients with free wall accessory pathways are shown in Table 1. The 15 patients with a left free wall accessory pathway who had left bundle-branch block aberration during reciprocating tachycardia all showed at least a 25 ms prolongation of the ventriculo-atrial interval during that aberration. However, none of the 12 patients with a left free wall accessory pathway who had right bundle-branch block aberration during reciprocating tachycardia had prolongation of the ventriculo-atrial interval during that aberration.

These observations are shown in Fig. 1 which shows reciprocating tachycardia in a patient with a left free wall accessory pathway (Case 3, Table 1) proven by epicardial mapping. During reciprocating tachycardia with normal conduction and right bundle-branch block, the ventriculo-atrial intervals are identical. In reciprocating tachycardia with left bundle-branch block, the ventriculo-atrial interval is prolonged by 50 ms. Minor variations in cycle length are caused by variations in the AH interval. Three patients with right free wall accessory pathways showed bundle-branch block during reciprocating tachycardia. Two of these three had right bundle-branch block aberration and their ventriculo-atrial intervals were prolonged by 30 and 55 ms. One had left bundle-branch block and there was no change in ventriculo-atrial interval.

Table 2 lists 4 patients in whom the site of accessory pathway was presumed to be septal based on results of epicardial mapping and the surgical incision. No patient had a ventriculo-atrial interval prolongation greater than 20 ms during bundle-branch block aberration.

In addition to providing useful information regarding the location of accessory pathways, the observation that bundle-branch block aberration during reciprocating tachycardia lengthens the

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[1] Designed by Michael Feezor, Ph.D., and built by Philip Talbert.

TABLE 1 *Bundle-branch block during reciprocating tachycardia in patients with free wall accessory pathways*

| *Case No.* | *RT with normal intraventricular conduction* | | | *RT with ipsilateral BBB* | | | *RT with contralateral BBB* | | | *Comment* |
|---|---|---|---|---|---|---|---|---|---|---|
| | *CL* | *HV* | *VA* | *CL* | *HV* | *VA* | *CL* | *HV* | *VA* | |
| | *Left free wall accessory pathways* | | | | | | | | | |
| 1 | 290 | 60 | 170 | 320 | 60 | 200 | 290 | 60 | 170 | |
| 2 | 335 | 35 | 190 | Did not occur | | | 355 | 35 | 190 | Initial study, |
| | 440 | NR | 140 | 480 | NR | 180 | Did not occur | | | restudy |
| 3 | 305 | 45 | 170 | 335 | 45 | 220 | 295 | 45 | 170 | |
| 4 | 280 | 40 | 180 | Did not occur | | | 280 | 40 | 180 | |
| 5 | 290 | 55 | 160 | 310 | 55 | 210 | Did not occur | | | |
| | 250 | 55 | 145 | Did not occur | | | 250 | 55 | 145 | Occurred later in same study |
| 6 | 365 | 55 | 120 | Did not occur | | | 365 | 55 | 120 | |
| 7 | | 50 | 90 | | 80 | 215 | Did not occur | | | Measurement from single atrial echo |
| 8 | | 50 | 95 | Did not occur | | | | 50 | 95 | Measurement from single atrial echo |
| 9 | 285 | 25 | 135 | Did not occur | | | 285 | 25 | 135 | |
| 10 | 300 | 35 | 175 | Did not occur | | | 300 | 35 | 175 | |
| 11 | 270 | 60 | 140 | 310 | 60 | 215 | 265 | 60 | 140 | |
| 12 | 275 | 45 | 150 | 335 | 65 | 200 | 285 | 60 | 145 | |
| 13 | 300 | 65 | 140 | Did not occur | | | 295 | 60 | 150 | |
| 14 | 290 | 55 | 160 | 335 | 75 | 220 | Did not occur | | | |
| 15 | 350 | 50 | 150 | 385 | 50 | 185 | Did not occur | | | |
| | *Right free wall accessory pathways* | | | | | | | | | |
| 16 | 305 | 50 | 190 | 340 | 50 | 225 | Did not occur | | | |
| 17 | 470 | 45 | 190 | Did not occur | | | 470 | 45 | 190 | |
| 18 | 340 | 45 | 160 | 375 | 45 | 225 | Did not occur | | | |

NR=not recorded.

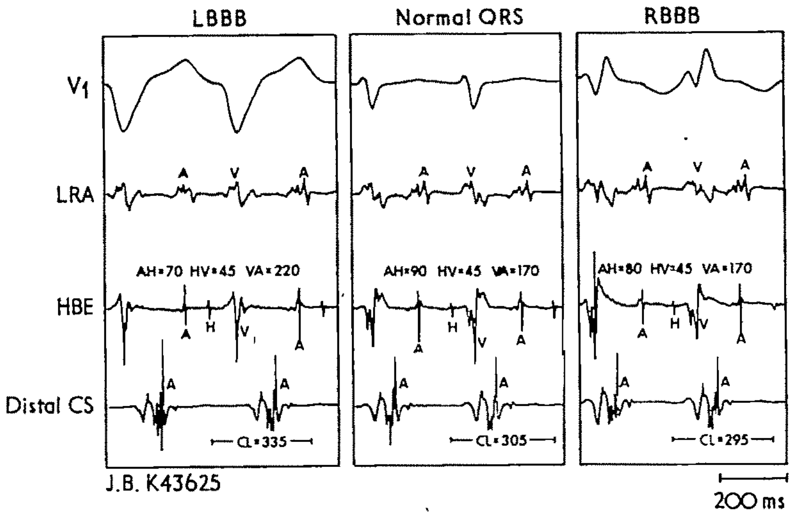

FIG. 1 *Electrophysiological studies during reciprocating tachycardia in a patient with a left free wall accessory pathway. From top to bottom are standard lead V1 (V1), and electrograms from the low lateral right atrium (LRA), His bundle (HBE), and distal coronary sinus (Distal CS). During reciprocating tachycardia with left bundle-branch block aberration, ventriculo-atrial conduction time increased by 50 ms over that observed during reciprocating tachycardia with normal intraventricular conduction and right bundle-branch block aberration. Note that local ventriculo-atrial interval measured in CS does not change with QRS configuration changes. Cycle length discrepancies are caused by variation in AH and HV intervals. Fig. 3, 4, and 5 are labelled similarly.*

TABLE 2 *Bundle-branch block during reciprocating tachycardia in patients with septal accessory pathways*

| *Case No.* | *Normal intraventricular conduction* | | | *RBBB* | | | *LBBB* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *CL* | *HV* | *VA* | *CL* | *HV* | *VA* | *CL* | *HV* | *VA* |
| 19 | 275 | 50 | 150 | 275 | 50 | 150 | Did not occur | | |
| 20 | 280 | 40 | 190 | 280 | 40 | 190 | Did not occur | | |
| 21 | 270 | 40 | 135 | 290 | 40 | 155 | 270 | 40 | 135 |
| 22 | 260 | 50 | 130 | Did not occur | | | 275 | 50 | 145 |

ventriculo-atrial interval may provide evidence for the existence of bypass tracts with unidirectional retrograde (ventriculo-atrial) conduction properties (Coumel and Attuel, 1974; Neuss *et al.,* 1975; Zipes, DeJoseph, and Rothbaum, 1974; Spurrell, Krikler, and Sowton, 1974). Fig. 2 is the 12 lead electrocardiogram from Case 15 (Table 1). There was no evidence for ventricular pre-excitation at rest or after pacing at multiple atrial sites. Fig. 3 shows simultaneous surface and intracardiac electrograms recorded during reciprocating tachycardia in this patient. The left panel shows tachycardia with left bundle-branch block and cycle length 385 ms. The right panel shows the same paroxysm after spontaneous reversion to reciprocating tachycardia with normal intraventricular conduction. There was a simultaneous decrease in the cycle length of reciprocating tachycardia to 350 ms. Measurement of the respective intervals within the cardiac cycle showed that shortening of the cycle length was entirely at the expense of the ventriculo-atrial interval. These observations, presented in detail elsewhere (Tonkin *et al.,* 1975b), support the conclusion that a left free wall accessory pathway with antegrade block participated in the reciprocating tachycardia. This patient has subsequently undergone epicardial mapping and operation which confirmed the location of the pathway.

Failure to define which segment of the cardiac cycle accounts for the increase in cycle length may give misleading information. Fig. 4 was taken from the records of a patient with frequent tachycardia whose 12 lead electrocardiogram showed intermittent ventricular pre-excitation. The left panel shows tachycardia with left bundle-branch block and cycle length 395 ms. The right panel shows tachycardia with normal QRS and cycle length 365 ms. This observation might suggest that a left-sided accessory pathway participated in the tachycardia (Coumel and Attuel, 1974). However, measurement of the timing of intracardiac events showed that the 30 ms change in cycle length accompanying left bundle-branch block was entirely accounted for by an increase in the HV interval from 65 to 95 ms, while the ventriculo-atrial interval remained unchanged (135 ms). This prolongation of the HV interval, therefore, became a pivotal piece of evidence showing that the distal conduction system participated in the reciprocating tachycardia

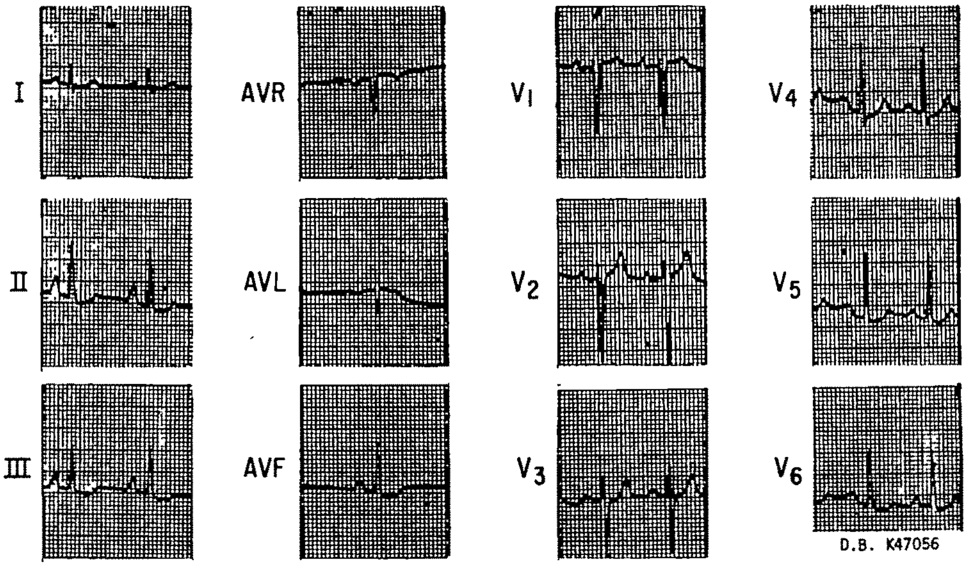

FIG. 2 *Twelve lead electrocardiogram showing no pre-excitation in a patient with an accessory pathway which sustained only retrograde conduction.*

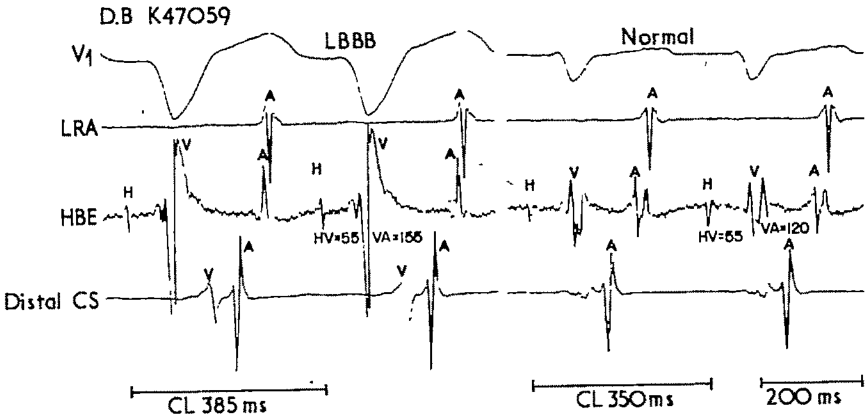

FIG. 3 *Increase in cycle length of reciprocating tachycardia from 350 ms to 385 ms during left bundle-branch block aberration was caused by prolongation of the ventriculo-atrial interval, suggesting the presence of left ventricular accessory pathway. This is from the same patient whose electrocardiogram is shown in Fig. 2.*

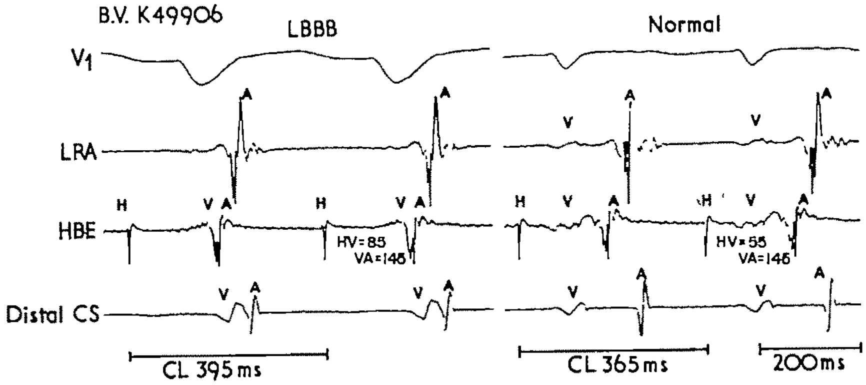

FIG. 4 *Increase in cycle length of reciprocating tachycardia during left bundle-branch block aberration caused by prolongation of HV interval. Failure to measure HV and ventriculo-atrial intervals would lead to false conclusion that there was a left lateral accessory pathway. The accessory pathway was in the septum.*

However, the absence of any change in the ventriculo-atrial interval argued against a left free wall accessory pathway. Atrial activation during reciprocating tachycardia and ventricular pacing began at the atrial septum and spread simultaneously to the left and right atria. This sequence is compatible with reciprocating tachycardia during either atrioventricular node re-entry or participation of a septal accessory pathway (Gallagher *et al.*, 1975; Gallagher *et al.*, 1976). It was, therefore, concluded that the reciprocating tachycardia was passing in an antegrade direction through the AV node and His-Purkinje system and returning by a septal accessory pathway to the atrium.

Fig. 5 shows portions of a single episode of reciprocating tachycardia from another patient who showed normal intraventricular conduction, left bundle-branch block aberration, and right bundle-branch block aberration. The cycle length was identical in all 3 forms of intraventricular conduction. However, during left bundle-branch block aberration the ventriculo-atrial interval increased by 35 ms and the AH interval decreased by the same amount. If cycle length only had been measured

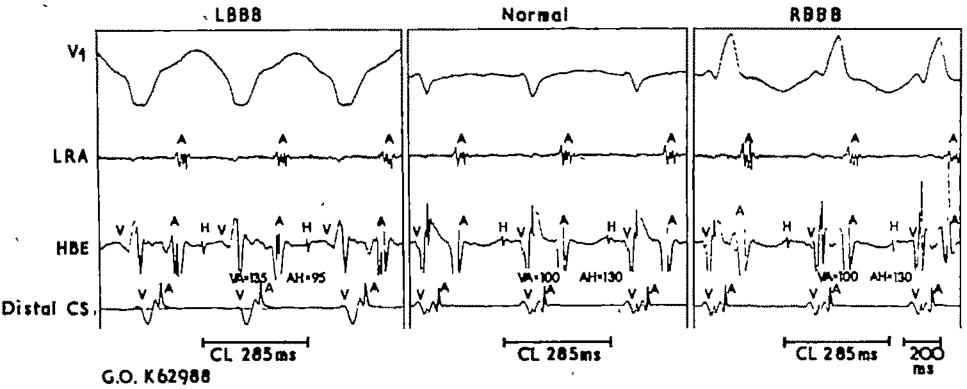

FIG. 5 *Failure of cycle length of reciprocating tachycardia to change during left bundle-branch block in a patient with a left free wall accessory pathway. Increase in ventriculo-atrial interval was compensated by identical decrease in AH interval. Lack of cycle length change by itself suggested AV nodal re-entry or participation of a septal accessory pathway as the mechanism for reciprocating tachycardia, but increase in ventriculo-atrial interval during left bundle-branch block confirms participation of a left free wall pathway.*

this tachycardia would have erroneously been diagnosed as being the result of AV node re-entry or of re-entry over a septal accessory pathway. The sequence of atrial activation during reciprocating tachycardia was again consistent with participation of a left free wall accessory pathway.

## Discussion

As surgical treatment of the potentially fatal or medically uncontrollable arrhythmias which are associated with the Wolff-Parkinson-White syndrome becomes more common, correct interpretation of observations which localize accessory pathways will become more important. One such observation is the change in AH, HV, and ventriculo-atrial intervals in reciprocating tachycardia with aberrant conduction as compared with these measurements during reciprocating tachycardia with normal intraventricular conduction. These intervals may be useful in several ways:

### (1) Evidence suggesting that an accessory pathway participates in reciprocating tachycardia

Prolongation of either the HV or ventriculo-atrial intervals in reciprocating tachycardia during aberrant intraventricular conduction supports the conclusion that the ventricular myocardium (then the accessory pathway) is a link in the re-entrant circuit. Prolongation of the ventriculo-atrial interval during reciprocating tachycardia caused by re-entry in the AV node is known to occur as the site of re-entry changes (Goldreyer and Bigger, 1971). If this prolongation occurred by coincidence simultaneously with the development of functional bundle-branch block, the result would mimic the events described here. Such a coincidence must be rare and far less common than if the ventriculo-atrial prolongation is caused by the functional bundle-branch block, which is the case in reciprocating tachycardia occurring over an accessory pathway.

### (2) Differentiation between free wall and septal accessory pathways

The observation of changes in ventriculo-atrial interval with intermittent bundle-branch block in reciprocating tachycardia represents a potentially useful method for separating patients with septal accessory pathways from those with free wall accessory pathways. This separation is of importance because surgical interruption of accessory pathways in the septum is technically more difficult (Gallagher *et al.*, 1975). In the small group of patients reported here, ventriculo-atrial interval prolongation of 25 ms or more during bundle-branch block in reciprocating tachycardia occurred only in the presence of a free wall accessory pathway in the ventricle with bundle-branch block. Case 22 (Table 2) is of particular interest. Before operation, the accessory pathway was thought to be located just to the left crux. A dissection of this area failed to abolish pre-excitation. The septum was not dissected because of the risk of developing complete heart block. It was concluded that the accessory pathway was either in the septum or in the epicardial fat behind the crux.

### (3) Recognition of accessory pathways with antegrade block

There are unusual cases in which accessory pathways have unidirectional antegrade block but support retrograde conduction in reciprocating tachycardia (Coumel and Attuel, 1974; Neuss *et al.*, 1975; Zipes *et al.*, 1974; Spurrell *et al.*, 1974; Tonkin *et al.*, 1975b). In these cases, the observation that the ventriculo-atrial interval during reciprocating tachycardia prolongs with bundle-branch block may be regarded as proof of participation of the accessory pathway in the re-entry circuit.

To provide data that are diagnostically useful for these purposes, it is important to measure not only cycle length changes but also the AH, HV, and ventriculo-atrial intervals during reciprocating tachycardia. This is illustrated in Fig. 4 and 5. Casual inspection of cycle length change in Fig. 4 suggests the participation of a left free wall accessory pathway in reciprocating tachycardia. However, the ventriculo-atrial interval did not change when left bundle-branch block occurred. The sequence of atrial activation during ventricular pacing and reciprocating tachycardia confirmed the presence of a septal accessory pathway. Similarly, Fig. 5 would be misinterpreted if only the cycle length were measured. In reciprocating tachycardia with left bundle-branch block aberration the ventriculo-atrial interval increased by 35 ms. Simultaneously the AH interval decreased by 35 ms, perhaps because the increased duration of the ventricular segment of the tachycardia pathway allowed recovery of the partially refractory AV node.

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# Effects remaining after withdrawal of long-term beta-receptor blockade

## *Reduced heart rate and altered haemodynamic response to acute propranolol administration*[1]

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*Central haemodynamics at rest and during exercise were studied in 14 male patients with moderate essential hypertension. Their circulatory state was studied before and immediately after intravenous administration of propranolol, 0·2 mg/kg body weight. In 8 of the patients an identical study was repeated after ≥2 months of oral propranolol therapy. This second study was performed when the oral therapy had been discontinued for ≥72 hours which exceeds the time necessary for complete metabolism and excretion of propranolol. Pulmonary oxygen uptake, arteriovenous oxygen difference, heart rate, and blood pressures in the subclavian artery, pulmonary artery, pulmonary wedge position, and right atrium were measured.*

*Before oral treatment, propranolol injection caused significant reductions of oxygen uptake (~5%), heart rate (~13%), cardiac output (~20%), and stroke volume (~10%), significant increments to systemic (~35%) and pulmonary vascular resistance (~35%), and increased filling pressures for both ventricles during exercise. After long-term treatment and omission of the drug, the spontaneous heart rates at rest and during exercise were significantly lower than before treatment. Propranolol injection now still increased the ventricular filling pressures at exercise but caused no significant effects on oxygen uptake, heart rate, cardiac output, stroke volume, or systemic vascular resistance.*

*It is concluded that long-term beta-receptor blockade leads to a physiological adaptation including a persistent relative bradycardia and almost complete abolition of the haemodynamic response to acute administration of a beta-receptor blocking agent. It is suggested that this adaptation, which resembles that of physical training, constitutes one mechanism whereby long-term beta-receptor blockade is able to reduce the arterial blood pressure.*

Although beta-adrenergic blocking drugs have been frequently used for treatment of arterial hypertension in recent years, it seems that the mechanisms underlying the observed antihypertensive effect are still not fully understood. Several investigations have shown that the fall in cardiac output and heart rate at acute inhibition of the beta-receptors is fully compensated for by a reflexogenic rise in systemic vascular resistance, which prevents any blood pressure fall (Frohlich *et al.*, 1968; Ulrych *et al.*, 1968 and others). The desired reduction in blood pressure has been found to require a prolonged beta-receptor blockade, extended over weeks or months (Prichard and Gillam, 1969; Tibblin and Åblad, 1969; Tarazi and Dustan, 1972 and others). Thus, the antihypertensive effect is not directly bound to the pharmacological action of blocking the beta-adrenergic receptors, but rather represents one feature in a pattern of physiological reset mechanisms occurring in response to prolonged beta-receptor blockade (cf. Prichard and Gillam, 1966; Frohlich *et. al.*, 1968). However, up till now our knowledge about long-term effects of beta-receptor

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TABLE 1 *Anthropometric data, blood volume calculated from body size ($BV_{calc}$), blood volume observed ($BV_{obs}$), heart volume (HV), and sphygmomanometric blood pressures (BP) obtained before the study started in I: 14 patients investigated before long-term treatment with propranolol, II: 8 patients investigated both before and after long-term treatment with propranolol*

| | | *Age* *(y)* | *Height* *(cm)* | *Weight* *(kg)* | $BV_{calc}$ *(l)* | | $BV_{obs}$ *(l)* | *HV* *(ml)* | *BP* *(mmHg)* *Systolic* | *Diastolic* |
|---|---|---|---|---|---|---|---|---|---|---|
| I | Mean | 43 | 179 | 91 | 6·7 | —*— | 5·5 | 855 | 194 | 119 |
| | SE | 3 | 2 | 4 | 0·2 | | 0·2 | 54 | 7 | 4 |
| II | Mean | 45 | 175 | 87 | 6·4 | —*— | 5·4 | 771 | 199 | 121 |
| | SE | 4 | 2 | 4 | 0 3 | | 0·4 | 41 | 8 | 3 |

*$P < 0{\cdot}001$.

blockade is sparse and it is now known for certain whether any delayed haemodynamic effects remain after withdrawal of prolonged beta-blocking therapy.

In the present investigation the acute haemodynamic effects of intravenous propranolol administration were studied in hypertensive patients before and after long-term oral treatment with the drug. In order to isolate delayed effects, the second study was performed after omission of the oral medication.

## Subjects and methods

Fourteen male patients aged 19 to 55 years with slight to moderate arterial hypertension were studied. They were informed of the nature, purpose, and possible risks involved in the study before giving their voluntary consent to participate. Anthropometric data, circulatory dimensions, and sphygmomanometric blood pressures obtained at the out-patient clinic before admission for the haemodynamic studies are given in Table 1. All the patients had 'primary hypertension' group I-II according to the WHO classification. Seven of them had never been treated with antihypertensive drugs. The others had received various antihypertensive treatment for short periods. In only 2 patients had beta-blocking drugs been used earlier, the treatment being terminated several months before this study was undertaken. None of the patients had any known renal disease or showed significantly reduced creatinine clearance. Neither was there any history of angina pectoris. All the patients had normal electrocardiograms both at rest and during heavy exercise. Physical working capacity was within normal limits. Eleven of the patients were overweight by 13 to 65 per cent (according to Metropolitan Life Insurance Tables, 1959). Consequently, the circulatory dimensions represented by the blood volume, total haemoglobin, and heart volume were significantly smaller than those calculated according to body size (cf. Sjöstrand, 1949). In relation to total haemoglobin the heart volumes were all within normal limits (Kjellberg, Rudhe, and Sjöstrand, 1949; Holmgren and Ovenfors, 1960).

The patients were admitted to the hospital 1 to 3 days before the first haemodynamic study. After this the long-term oral propranolol therapy was instituted and the patients were checked regularly in the out-patient clinic. Their daily doses of propranolol ranged between 160 and 640 mg. The blood pressure reaction to this therapy, as judged from sphygmomanometric measurements, was a significant reduction of both systolic and diastolic pressure. Eight of the patients accepted an additional haemodynamic study after the long-term treatment for 2 to 9 months. The trial design is presented in Fig. 1. At admission after the oral treatment the sphygmomanometric arterial pressures were significantly reduced ($P < 0{\cdot}05$), now being only slightly raised (~155/95 mmHg (20·6/12·6 kPa) compared with ~200/120 mmHg (26·6/16·0 kPa) before treatment). At admission the therapy was discontinued immediately. The patients had no drugs for ≥72 hours before the second haemodynamic study was performed. During the

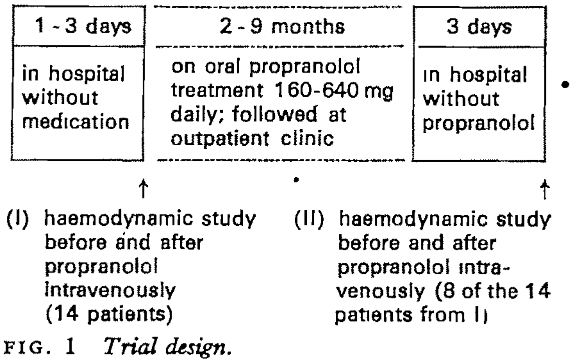
1 - 3 days
in hospital without medication
2 - 9 months
on oral propranolol treatment 160-640 mg daily; followed at outpatient clinic
3 days
in hospital without propranolol
(I) haemodynamic study before and after propranolol intravenously (14 patients)
(II) haemodynamic study before and after propranolol intravenously (8 of the 14 patients from I)

FIG. 1 *Trial design.*

time after omission of the drug the blood pressure was measured repeatedly; none of the patients showed any abrupt pressure rise in direct response to this omission of the drug.

Blood volume was determined by conventional $^{131}$I-albumin technique (Fine and Seligman, 1943; Pritchard, Moir, and MacIntyre, 1955). Heart volume was determined by the two-plane *x*-ray method, performed with the patient supine (Larsson and Kjellberg, 1948). Sphygmomanometric blood pressure was measured according to the Korotkow method, diastolic value noted at phase 5.

## Haemodynamic studies

A radio-opaque 'teflon' catheter (1·2 mm outer diameter) was inserted percutaneously under local anaesthesia into the left brachial artery and passed to a tip position in the subclavian artery. A double lumen catheter (Swan-Ganz 7F, Edwards Laboratories) was inserted percutaneously into an antecubital vein and passed to the pulmonary artery under fluoroscopic guidance. Pulmonary oxygen uptake, arteriovenous oxygen difference, heart rate, and blood pressures were measured at rest and during bicycle exercise of 7 minutes at work loads preset individually to increase heart rate to about 120 to 130 beats/min. The entire procedure was performed with the patients in supine body position. After a resting period of 20 to 30 minutes, baseline measurements were repeated and propranolol was then given intravenously (0·2 mg/kg body weight). After a further 7-minute period, the resting measurements and the exercise programme were repeated.

## Technical procedures

The expired air was collected in Douglas bags for determination of pulmonary oxygen uptake (Scholander, 1947). Blood samples were drawn from the pulmonary and brachial arteries for analysis of oxygen content (Holmgren and Pernow, 1959). Cardiac output was calculated by the direct Fick method. The expired air was collected for 5 minutes at rest and for 3 minutes during exercise. Blood pressures were recorded in the subclavian artery, in the pulmonary wedge position, in the pulmonary artery, and in the right atrium by means of electrical transducers (EMT 34 and 35, Elema) and referred to standard water columns corresponding to 20, 50, and 100 mmHg (2·7, 6·7, and 13·3 kPa), respectively. Systemic vascular resistance was calculated as the ratio between the mean blood pressure fall from the subclavian artery to the right atrium and the value for cardiac output. The pulmonary vascular resistance was calculated similarly using the mean pressure fall from the pulmonary artery

TABLE 2 *Haemodynamic results from 14 male hypertensive patients at rest, during exercise, and 20 minutes after exercise without pretreatment and at rest and during exercise after intravenous administration of propranolol (0·2 mg/kg b.w.) (mean ± SEM)*

| | *No treatment* | | | *During beta-receptor blockade* | |
|---|---|---|---|---|---|
| | *Rest* | *Exercise* | *Rest 20 minutes after exercise* | *Rest* | *Exercise* |
| Oxygen uptake (ml/min) | 319 ± 14 | 1279 ± 77 | 325 ± 11 | 301 ± 14 | 1214 ± 82 |
| Arteriovenous $O_2$ diff. (ml/1) | 49 ± 2 | 103 ± 3 | 51 ± 2 | 58 ± 2 | 129 ± 5 |
| Cardiac output (1/min) | 6·7 ± 0·5 | 12·5 ± 0·7 | 6·6 ± 0·5 | 5·4 ± 0·4 | 9·5 ± 0·6 |
| Heart rate (beats/min) | 74 ± 4 | 120 ± 5 | 66 ± 3 | 65 ± 1 | 99 ± 3 |
| Stroke volume (ml) | 93 ± 7 | 108 ± 7 | 98 ± 7 | 83 ± 5 | 96 ± 6 |
| Vasc. resist. (mmHg/1/min) | | | | | |
| Systemic | 18 ± 1 | 11 ± 1 | — | 23 ± 2 | 14 ± 1 |
| Pulmonary | 0·8 ± 0·1 | 0·9 ± 0·1 | — | 1·1 ± 0·1 | 1·2 ± 0·1 |
| Blood pressure (mmHg) | | | | | |
| Subclav. artery | | | | | |
| Systolic | 159 ± 5 | 182 ± 6 | — | 163 ± 6 | 177 ± 4 |
| Diastolic | 99 ± 3 | 108 ± 4 | — | 101 ± 3 | 103 ± 3 |
| Mean | 124 ± 4 | 142 ± 5 | — | 126 ± 4 | 133 ± 3 |
| Pulm. artery | | | | | |
| Systolic | 24 ± 2 | 45 ± 3 | — | 25 ± 2 | 52 ± 3 |
| Diastolic | 12 ± 1 | 22 ± 2 | — | 12 ± 1 | 29 ± 2 |
| Mean | 17 ± 1 | 33 ± 2 | — | 18 ± 2 | 39 ± 2 |
| Pulm. wedge | | | | | |
| Mean | 12 ± 1 | 21 ± 2 | — | 12 ± 1 | 27 ± 2 |
| Right atrium | | | | | |
| Mean | 6 ± 1 | 8 ± 1 | — | 7 ± 0 | 12 ± 1 |

*Conversion from Traditional Units to SI Units:* 1 mmHg≈0·133 kPa.

to the pulmonary wedge position. The mid-thoracic height was used as zero pressure level. The pressure traces were recorded on an ultraviolet beam writer (Ultralette, ABEM 5650). Heart rate was recorded continuously by electrocardiography. The room temperature was kept at about 23°C. Standard statistical methods were employed (Snedecor and Cochran, 1967), the paired t-test being used when applicable. Data in the text, tables, and figures are reported as mean ± standard error of mean.

## Results

### I: Fourteen patients studied before long-term oral treatment

**Haemodynamic status** Data obtained at rest and during exercise are given in Table 2. The normal limits from the material published by Ekelund and Holmgren (1967) have been used for reference.

At rest pulmonary oxygen uptake exceeded estimates based on age and body size by about 24 per cent. In relation to oxygen uptake the mean values for arteriovenous oxygen difference and cardiac output were within the normokinetic limits. In relation to cardiac output, the mean values for systolic, diastolic, and mean pressures in the subclavian artery considerably exceeded the normal values. Thus, the mean calculated systemic vascular resistance was enhanced. The filling pressures for both the ventricles were within the normal variations, as were the systolic and mean pressures in the pulmonary artery.

During exercise mean oxygen uptake showed a fourfold increase. The mean rise in arteriovenous oxygen difference and cardiac output were within the normal range. All the patients thus fell within the normokinetic limits. The stroke volume increased significantly, by about 16 per cent compared with resting values. The pressures in the subclavian artery showed only minimum changes compared with those at rest, still being higher than normal in relation to cardiac output. The mean systemic vascular resistance was lower than at rest, but still higher than normal. In the pulmonary artery the systolic, mean, diastolic, and wedge pressures rose above the normal limits. The mean filling pressure for the right ventricle was maintained at an ordinary level.

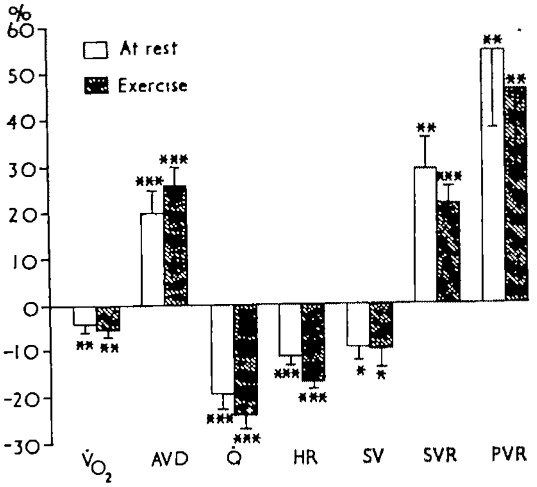

FIG. 2 *Acute effects of intravenous propranolol (0·2 mg/kg b.w.) on pulmonary oxygen uptake ($\dot{V}_{O_2}$), arteriovenous oxygen difference (AVD), cardiac output ($\dot{Q}$), heart rate (HR), stroke volume (SV), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) at rest and during exercise in 14 male hypertensive patients. Mean percentage effects. Bars indicate SEM. Asterisks indicate statistical significance for each column.*

**Acute effects of intravenous propranolol administration** Data are presented in Table 2 and Fig. 2

After administration of propranolol cardiac output was considerably reduced. This effect was most pronounced during exercise, both in absolute values and in relation to oxygen uptake. The magnitude of the cardiac output suppression was similar to that described previously (Åström, 1968).

The oxygen uptake was significantly reduced by about 5 per cent at propranolol injection both at rest and during exercise. A similar effect was found in healthy individuals (Brundin, to be published). The heart rate was significantly retarded, most conspicuously during exercise (–17%).

The stroke volume was significantly smaller (–10%) after propranolol. This effect was noted even during exercise, in contrast to previous results in healthy subjects and in patients with angina pectoris (cf. Åström, 1968). However, the exercise-induced increase in stroke volume (about 14%) was still found after propranolol.

Systemic vascular resistance was considerably increased after propranolol injection both at rest (~28%) and during exercise (~22%). The pressure in the systemic artery was not significantly affected by propranolol at rest. During exercise the mean arterial pressure was lower (–7%) after propranolol. At rest the pressures in the pulmonary artery, pulmonary wedge position, and right atrium were essentially unaffected by propranolol. During exercise, however, the filling pressures for both the

TABLE 3 *Haemodynamic results obtained before and after i.v. administration of propranolol 0·2 mg/kg b.w. in 8 male hypertensive patients before and after long-term oral therapy with propranolol (mean values ±SE)*

| | *Before long-term treatment* | | | | *After long-term treatment* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Rest* | | *Exercise* | | *Rest* | | *Exercise* | |
| | *Spontaneous* | *After propranolol* | *Spontaneous* | *After propranolol* | *Spontaneous* | *After propranolol* | *Spontaneous* | *After propranolol* |
| Oxygen uptake (ml/min) | 322±22 | 311±18 | 1268±130 | 1215±139 | 296±12 | 292±12 | 1287±125 | 1260±141 |
| Arteriovenous $O_2$ diff. (ml/l) | 46±2 | 58±3 | 105±4 | 129±8 | 53±4 | 56±3 | 114±5 | 125±5 |
| Cardiac output (l/min) | 7·3±0·7 | 5·5±0·5 | 12·0±0·9 | 9·5±1·0 | 6·0±0·4 | 5·4±0·4 | 11·3±0·9 | 10·1±1·1 |
| Heart rate (beats/min) | 83±5 | 71±4 | 130±5 | 105±4 | 66±4 | 64±3 | 105±6 | 94±2 |
| Stroke volume (ml) | 91±10 | 78±6 | 95±8 | 88±8 | 95±9 | 87±10 | 110±9 | 105±10 |
| Vasc. resist. (mmHg/l/min) | | | | | | | | |
| Systemic | 18±2 | 26±3 | 12±1 | 15±2 | 20±2 | 23±3 | 13±1 | 14±2 |
| Pulmonary | 0·7±0·1 | 1·1±0·2 | 0·8±0·1 | 1·1±0·1 | 0·9±0 1 | 1·3±0·2 | 1·1±0·2 | 1·2±0 2 |
| Blood pressure (mmHg) | | | | | | | | |
| Subclav. artery | | | | | | | | |
| Systolic | 158±7 | 172±7 | 188±8 | 181±5 | 154±8 | 161±15 | 187±10 | 181±11 |
| Diastolic | 98±5 | 107±4 | 113±6 | 104±3 | 94±5 | 97±8 | 102±6 | 102±6 |
| Mean | 126±5 | 133±5 | 144±7 | 134±4 | 119±7 | 121±9 | 139±8 | 133±8 |
| Pulm. artery | | | | | | | | |
| Systolic | 23±2 | 26±4 | 42±4 | 52±4 | 26±2 | 26±2 | 44±4 | 47±3 |
| Diastolic | 11±1 | 12±2 | 21±3 | 29±2 | 12±1 | 11±1 | 20±2 | 25±2 |
| Mean | 16±2 | 18±2 | 31±3 | 39±3 | 18±1 | 18±2 | 32±3 | 37±3 |
| Pulm. wedge | | | | | | | | |
| Mean | 10±2 | 11±3 | 20±4 | 27±2 | 11±1 | 12±1 | 18±4 | 25±2 |
| Right atrium | | | | | | | | |
| Mean | 6±1 | 7±0 | 8±1 | 13±1 | 6±1 | 6±1 | 7±1 | 12±1 |

ventricles rose above normal limits, significantly more than before propranolol, as did the systolic and mean pressures in the pulmonary artery. Thus, the acute effects of propranolol could be summarized as follows: (a) reduction of oxygen uptake, cardiac output, heart rate, and stroke volume; (b) further increase of systemic and pulmonary vascular resistance; (c) increase of the pressures in the pulmonary artery and of the filling pressures for both ventricles during exercise.

## II: Eight patients studied before and after long-term oral therapy with propranolol

The haemodynamic status did not differ significantly from that found in the larger group. Data are given in Table 3 and Fig. 3 and 4. Thus, the systemic vascular resistance and arterial blood pressures were raised both at rest and during exercise and the filling pressure for the left ventricle rose steeply during exercise.

The acute effects of propranolol injection were also essentially identical with those in the larger group.

After long-term treatment the spontaneous heart rates at rest and during exercise were significantly lower ($P < 0{\cdot}05$) than before oral treatment. The mean values for pulmonary oxygen uptake, cardiac

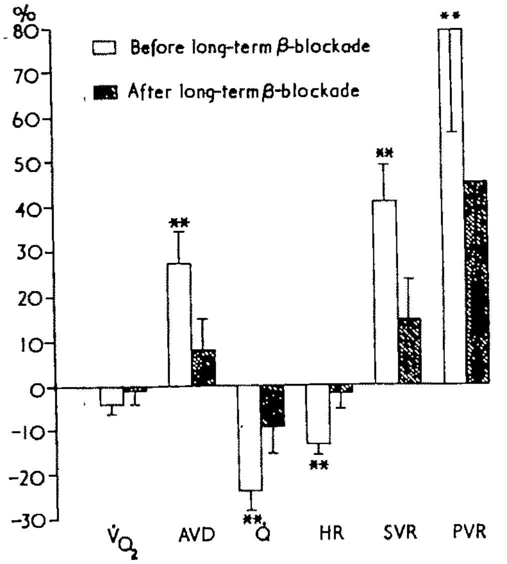

FIG. 3 *Acute haemodynamic effects of intravenous propranolol (0·2 mg/kg b.w.) at rest in 8 male hypertensive patients studied before and after long-term oral propranolol therapy. Mean percentage effects. Bars indicate SEM. Abbreviations as in Fig. 2. Asterisks indicate statistical significance for each column.*

output, and arterial blood pressures tended to be somewhat lower than before the long-term treatment, but none of these variables had changed significantly during the period of oral beta-receptor blockade. Neither was vascular resistance altered compared with the pretreatment investigation.

Intravenous injection of propranolol now caused only minor haemodynamic effects, none of which attained statistical significance at rest. During exercise, propranolol injection caused slight and nonsignificant reductions in cardiac output and mean arterial blood pressure. Neither was the systemic vascular resistance significantly changed by propranolol injection (Fig. 4). However, during exercise the filling pressures for both ventricles increased in response to the intravenous beta-blockade in a similar way to that observed before long-term treatment (Table 3). However, most of the acute haemodynamic effects of intravenous propranolol injection were considerably reduced or abolished after long-term treatment with the drug.

## Discussion

The present investigation was undertaken in order to study acute and any chronic effects of beta-adrenergic receptor blockade. The study was designed to find out whether any haemodynamic effects persisted after a period of long-term receptor blockade and whether the acute effects of propranolol administration were different or modified after the long-term treatment.

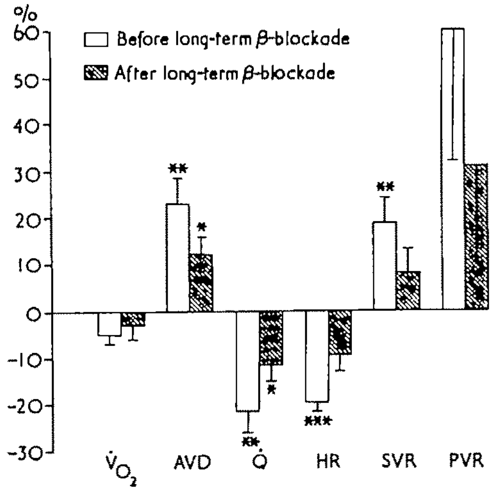

FIG. 4 *Acute haemodynamic effects of intravenous propranolol (0·2 mg/kg b.w.) during exercise in 8 male hypertensive patients studied before and after long-term oral propranolol therapy. Mean percentage effects. Bars indicate SEM. Abbreviations as in Fig. 2 and 3. Asterisks indicate statistical significance for each column.*

The patients in this study were all young or middle-aged men with slight or moderate essential hypertension. All except three had an increased body weight. Apart from the high arterial pressure and systemic vascular resistance, their haemodynamic status was normal compared with previously published normal materials (Ekelund and Holmgren, 1967).

The acute haemodynamic effects in response to propranolol injection before long-term treatment with the drug could be explained easily in most respects as secondary to the well-known negative chronotropic and inotropic effects that occur in immediate response to inhibition of the beta-adrenergic receptors of the heart (Nickerson, 1949). The negative chronotropic effect reduces cardiac output provided there is no compensatory increase in stroke volume. Such an increase will probably be prevented by the concomitant negative inotropic effect. In the present study propranolol led to a significant reduction of stroke volume. Cardiac output consequently decreased. A simultaneous reduction of heart rate and cardiac output leads to less frequent and weaker stimuli to the baroreceptors. Thereby the afferent discharge frequency in the depressor nerves will fall. It is well known that such a reduction of this particular afferent nervous activity constitutes the adequate stimulus for the pressor area of the vasomotor centre and leads to an accelerated impulse traffic in the sympathetic nerves, increasing the release of noradrenaline at the nerve endings (for references see recent review by Sleight, 1975). The α-receptors of the resistance vessels will react to the increased stimulation and the peripheral vascular resistance will rise, thus preventing the fall of the mean arterial blood pressure which would otherwise follow a reduction of cardiac output.

During dynamic exercise, when the blood vessels in the muscles dilate and general vascular resistance falls, extra demands for an effective baroreceptor function will arise if the normal capacity for increasing cardiac output is impaired. Consequently, one would expect the mean arterial blood pressure to fall at exercise after propranolol administration: this it did significantly. A further physiological consequence of physical exercise is an increased return of venous blood to the heart. If the primary effect of beta-adrenergic inhibition is a depressant action on both the frequency and the force of the heart, the filling pressures would be expected to rise during exercise after propranolol administration: this they did considerably. These higher filling pressures had the secondary effect of facilitating the ventricular filling, which might well explain why the stroke volume rose in response to exercise even after propranolol injection. This effect was probably a result of the Frank-Starling mechanism, which would not be interfered with by the negative inotropic effect of the drug.

The significant increase in pulmonary vascular resistance which followed beta-receptor blockade both at rest and during exercise seems difficult to explain. Pulmonary dynamics, which might be involved in the mechanisms underlying regulation of vascular resistance, were not analysed in this study. Arterial oxygen saturation did not, however, change after propranolol.

In accordance with the view presented above, a therapeutic beta-receptor inhibition would, if extended over long periods, constitute a chronic load on the baroreceptor reflex mechanisms. Thus, a steady and intense stimulation would be directed from the vasomotor centre to the sympathetic nerves and further onto the adrenergic receptors. It is well known that most neurophysiological systems react to a long-lasting stimulation by some kind of adaptation (cf. Adair and Manning, 1975). It seems unlikely that such a complex neuronal and neurohumoral chain as that from the baroreceptors via the vasomotor centre and the sympathetic pre- and postganglionic neurons to the adrenergic receptors would be completely devoid of adaptive functions. However, during beta-receptor blockade of the heart, any adaptation in the afferent part of the baroreceptor reflex would not seem to be of much interest, since the cardiac effects at propranolol injection all constitute negative stimuli with regard to the baroreceptor as well as the afferent depressor nerve function. On the other hand, any adaptive mechanisms within the central relay neurons and/or in the sympathetic nerves would be relevant here. Even at receptor level, continuous neurohumoral stimulation has been shown to induce a subsensitivity (for ref. see Furchgott, 1972).

Such an adaptation in the vasomotor regulation system, which would be difficult to show directly in man, might well be a conceivable mechanism whereby the beta-receptor blocking drugs are able to reduce the arterial blood pressure. Some adaptive function has previously been suggested as the mechanism for the antihypertensive effect of beta-receptor blocking drugs (cf. Prichard and Gillam, 1966; Frohlich *et al.*, 1968; Tarazi and Dustan, 1972). The direct action of beta-receptor inhibition can never be expected to, and has never been shown to, reduce the blood pressure. It is known that long-term therapy is required before the blood pressure reduction appears (Prichard and Gillam, 1969 and others). This fact agrees with the view that a vegetative adaptation is needed to induce the hypotensive effects of beta-receptor blocking drugs.

The present results show that long-term inhibition of human beta-adrenergic receptors leads to an adaptation process, at least in those adrenergic mechanisms which are mediated by the 'beta side' of the receptor. This adaptation remains after the drug has been omitted, metabolized, and excreted. The persistent effects, which have not been described previously, appeared as: (1) a considerable reduction of heart rate; (2) an almost total lack of acute haemodynamic response to intravenous propranolol administration.

Both these effects were demonstrable at rest as well as during exercise. The spontaneous heart rate at rest was thus significantly lowered at the reinvestigation. The magnitude of this reduction, which occurred during and persisted after the long-term therapy, corresponds to that observed after long-lasting and intense physical training. The possible mechanisms whereby the heart rate can be depressed if not parallelled by increased dimensions of the central circulation, are either an increased parasympathetic or a decreased sympatho-adrenal influence on the heart. The finding that intravenous injection of propranolol did not change the heart rate significantly indicates that it was the sympatho-adrenal part of the autonomic heart rate regulation that was changed, either in the form of a reduced basal sympatho-adrenal activity or, perhaps, in the form of a persistent reduction of the sensitivity of the beta-adrenergic receptors of the heart. A reduced receptor sensitivity has been shown to occur after intense physical training (Brundin and Cernigliaro, 1975). In extremely well-trained athletes, beta-receptor blocking drugs have also been found to be completely without effect on the basal heart rate (Frick, Elovainio, and Somer 1967; Ekblom, Kilbom, and Soltysiak, 1973). Except for the heart rate, none of the variables studied at reinvestigation 72 hours after omission of the drug showed any significant changes compared with the results at the first investigation before the long-term therapy. The lack of acute propranolol effects was a general finding at the reinvestigation. Neither cardiac output nor vascular resistance was changed when a large dose of propranolol was administered intravenously. This general lack of effect might, however, be secondary to the lack of effect on heart rate. As described previously by several authors and discussed above, the bradycardia at beta-receptor blockade is probably of great importance as the mechanism underlying most of the other haemodynamic effects.

The lack of propranolol effect on the heart rate after long-term treatment seems to mimic a persistent beta-receptor blockade. This finding could be explained easily if 72 hours were too short a time for the elimination of propranolol from the heart tissue and its beta-receptors. The blood concentrations of propranolol were not measured in this study. However, previous pharmacological studies on the metabolism and elimination of propranolol from the body and from the heart have shown unequivocally that no active substance could be detected after 48 hours (Faulkner *et al.*, 1973).

The increased blood pressure in the pulmonary artery during exercise was one of the acute effects of propranolol injection which was only slightly reduced after long-term therapy with the drug. This indicates that during beta-receptor blockade the pressure work for the right ventricle was augmented in these patients. It is not known for certain whether this increased right ventricular load has any clinical consequences. However, except for patients with incipient heart failure, no previous clinical study seems to have identified right ventricular insufficiency as a major or regular complication during long-term treatment with beta-receptor blocking drugs.

In conclusion, this investigation has shown that in male patients with moderate hypertension, propranolol elicits acute haemodynamic effects at rest and during exercise which are probably secondary to the well-known negative chronotropic and inotropic effects of the drug. These effects were abolished or considerably reduced after oral treatment with propranolol. Furthermore, a previously unknown persistence of a relative bradycardia after withdrawal of long-term therapy with propranolol has been shown. On the basis of these findings a new concept is suggested for the mechanisms underlying the antihypertensive effect involving long-lasting inhibition of the beta-adrenergic receptors.

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# Developing cardiac rupture as initial sign of acute myocardial infarction

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*Pathological data are given of 4 patients in whom the development of cardiac rupture was the initial sign of myocardial infarction. The term 'concealed cardiac rupture' is proposed for this condition. In each instance the clinical diagnosis was 'onset of infarction', whereas the necropsy suggested that the acute onset of symptoms was caused by the start of rupture.*

*The arguments for classifying the cases as 'concealed rupture' are (1) the lack of correlation between histological and clinical dating of the infarct, (2) the observation that the tear may take considerable time before actual epicardial breakthrough occurs, and (3) the fact that a high percentage of infarcts may pass clinically unnoticed.*

Cardiac tamponade is at present an important cause of death in patients with acute myocardial infarction. At the coronary care unit of the department of cardiology an incidence of 27 per cent was found among patients who died of acute infarction (Lie, Roels-van Ijsseldijk, and Van Capelle, 1975). To the clinician the occurrence of cardiac rupture is often sudden and unexpected, since definite warning signs are not present. However, morphologists have previously suggested that the heart specimen often shows features indicative of a delayed rupture (Lautsch and Lanks, 1967). It has also been stated that occasionally a patient may present with symptoms of acute infarction, which actually represented the start of the rupture (Lautsch and Lanks, 1967; Van Tassel and Edwards, 1972). In a recent correlative study of 50 patients with cardiac tamponade this was confirmed (Becker and van Mantgem, 1975). The term 'concealed rupture' was proposed to indicate the circumstance in which such a lack of correlation existed between clinical symptomatology and morphological features. It is the purpose of this report to re-emphasize the occurrence of this phenomenon.

## Case reports

### Case 1

A 61-year-old woman was known to have hypertension for 7 years. She first complained of pain in the left arm after a minor traffic accident. Two days later she developed vague pain in the chest. However, after two more days she suddenly experienced severe chest pain and she collapsed. On immediate admission she was sweating. Physical examination revealed a systolic blood pressure of 70 mmHg and a heart rate of 110 per minute. The central venous pressure judged from the jugular veins was not raised. The electrocardiogram showed the signs of recent anterolateral myocardial infarction. She rapidly developed signs of cardiogenic shock. She was treated with lignocaine, but no anticoagulants were given. Sixteen hours after admission she suddenly died.

The necropsy showed a large transmural myocardial infarction in the anteroseptal wall of the left ventricle. It showed a central rupture which had led to a tamponade of 400 ml blood. At the site of rupture there was a distinct erosion of the necrotic myocardium (Fig. 1A). The actual tear was slit-like and located at the top of the erosion. Thrombus was covering the site of rupture and part of the eroded area. There was two-vessel disease of the coronary arteries, with total recent occlusion of both the anterior descending artery

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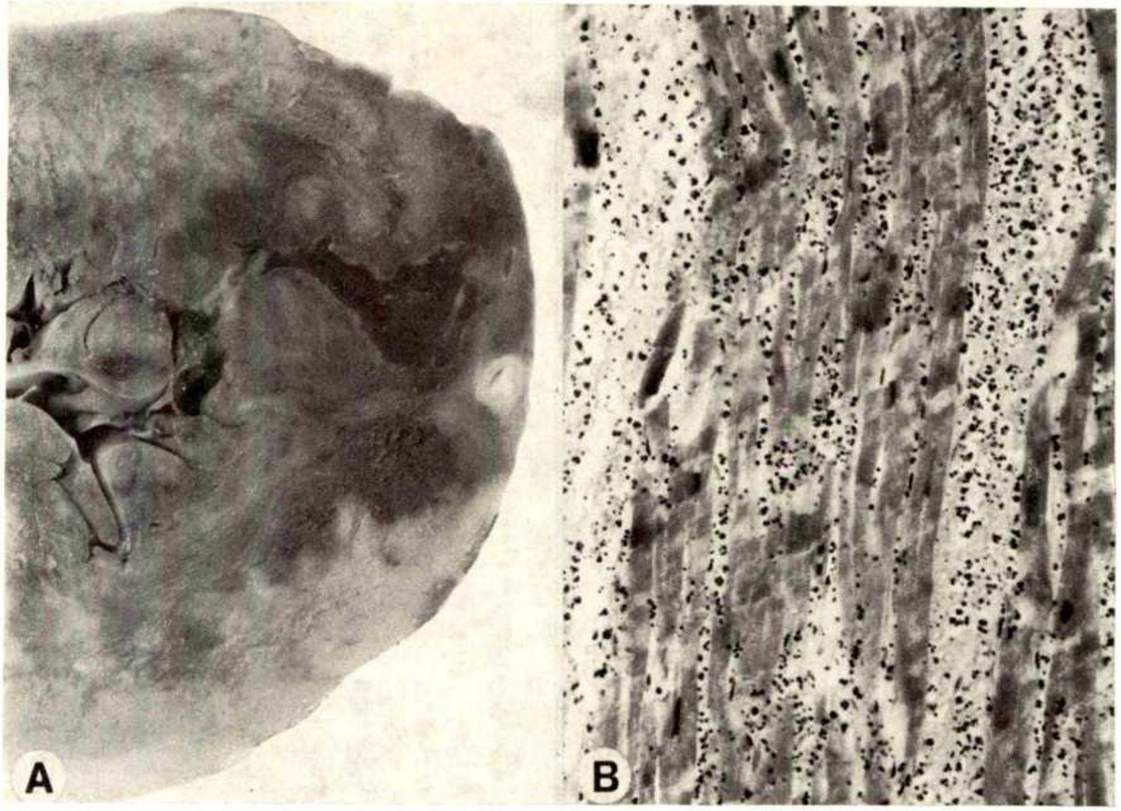

FIG. 1 *Case 1. The clinical dating of the infarct was 16 hours. (A) The gross aspect of part of the anterolateral wall of the left ventricle. The transmural infarct is seen. At the site of rupture an erosion of the affected myocardium has occurred. The actual epicardial breakthrough cannot be seen. (B) A representative microscopical section of the infarcted myocardium. There is massive infiltration of dead myocardium by polymorphonuclear leucocytes. This is not in agreement with an infarct of 16 hours' duration but, instead, suggests that the vague complaints two days before admission represented the onset of infarction. The erosion at the site of rupture indicates a slowly progressive tear. Therefore, the sudden onset of severe chest pain could have been caused by the onset of the rupture process. (Haematoxylin and eosin. ×200.)*

and the left circumflex branch.

Microscopical sections of the infarct showed a massive leucocytic infiltration of the necrotic myocardium, indicative of a myocardial infarction of a much older date than the 24 hours indicated by the clinical history (Fig. 1B). In retrospect, therefore, this patient probably experienced an infarction after her minor traffic accident, while the acute episode in effect represented the onset of rupture.

### Case 2

A 53-year-old man had complained for some weeks of intermittent chest pain, occasionally radiating towards the left arm. The pain was always related to periods of emotional disturbance. Four days before death he woke up in the middle of the night with severe chest pain, radiating to the left arm and accompanied by heavy sweating. He was admitted to hospital 4 hours later and on examination showed a blood pressure of 160/110 mmHg, with a heart rate of 100 per minute. His central venous pressure was not raised, as judged from the neck veins. The electrocardiogram showed recent inferior wall infarction. He was treated with lignocaine and he was given anticoagulants. The pain disappeared. The next day he developed signs of acute abdominal distress, for which no conclusive explanation was found. Three days later, that is 4

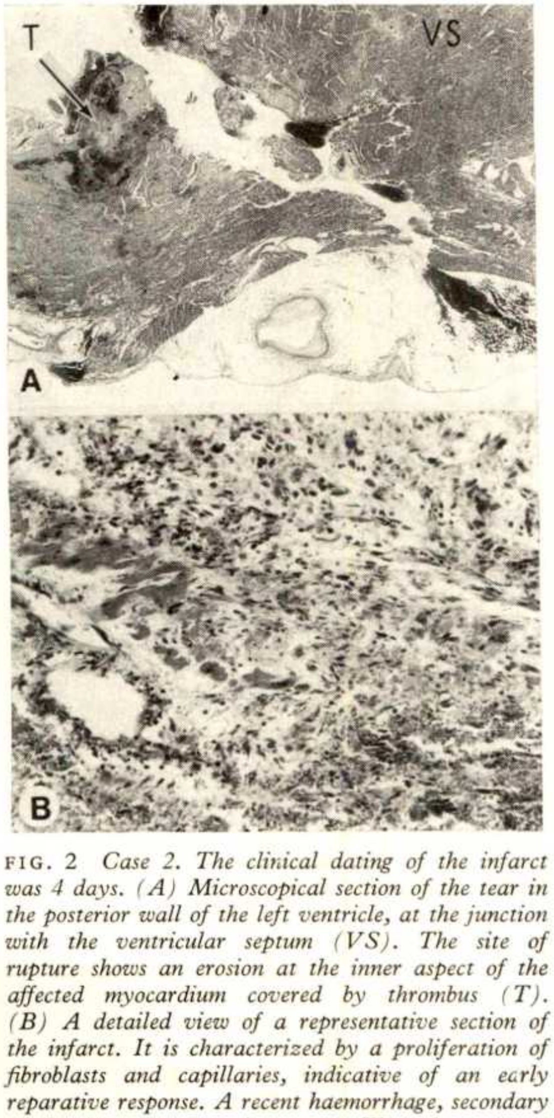

FIG. 2 *Case 2. The clinical dating of the infarct was 4 days. (A) Microscopical section of the tear in the posterior wall of the left ventricle, at the junction with the ventricular septum (VS). The site of rupture shows an erosion at the inner aspect of the affected myocardium covered by thrombus (T). (B) A detailed view of a representative section of the infarct. It is characterized by a proliferation of fibroblasts and capillaries, indicative of an early reparative response. A recent haemorrhage, secondary to the dissecting tear, is present. These features are not in agreement with an infarct of 4 days but, instead, fit an infarct of between 1 and 3 weeks old. In retrospect this could correlate with the patient's history. (Haematoxylin and eosin. A × 4·7, B × 165.)*

days after admission, he suddenly died.

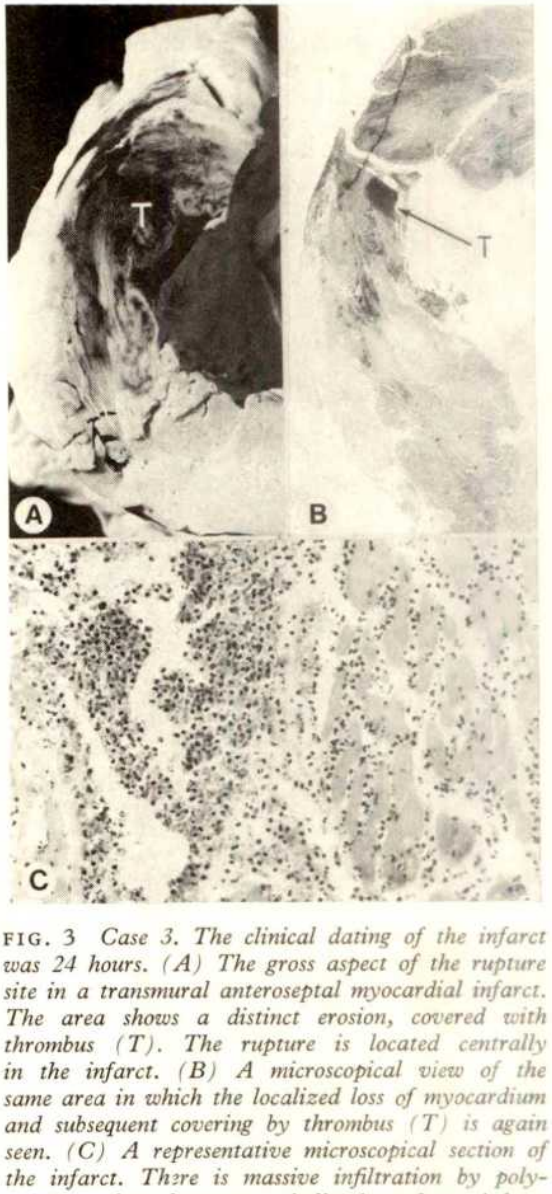

FIG. 3 *Case 3. The clinical dating of the infarct was 24 hours. (A) The gross aspect of the rupture site in a transmural anteroseptal myocardial infarct. The area shows a distinct erosion, covered with thrombus (T). The rupture is located centrally in the infarct. (B) A microscopical view of the same area in which the localized loss of myocardium and subsequent covering by thrombus (T) is again seen. (C) A representative microscopical section of the infarct. There is massive infiltration by polymorphonuclear leucocytes, indicative of an infarct older than 24 hours. (Haematoxylin and eosin. B × 2·0, C × 130.)*

The necropsy confirmed the presence of a large transmural inferior wall infarct, which extended from the apex to the base of the heart and also involved the posteromedial papillary muscle group. The heart had ruptured posteriorly, close to the ventricular septum (Fig. 2A). There was a tamponade of 500 ml blood. The coronary arteries showed two-vessel disease, with total occlusions distally in the right coronary artery and proximally in the anterior descending branch. There were no signs of previous myocardial infarctions.

The microscopy of the myocardium showed signs of an early reparative response with ingrowth of fibroblasts and capillaries (Fig. 2B). The cellular infiltrate was mainly composed of macrophages, carrying lipofuchsin and iron pigments, and these changes were consistent with an infarct of a somewhat older date than the 4 days judged from the clinical history. In fact, the histological dating suggests myocardial infarction of somewhere between 1 and 3 weeks earlier. Again the distinct discrepancy suggested concealed rupture, in a silent infarct. The sudden onset of symptoms 4 days before death could represent the onset of rupture. There were no signs of acute infarction.

### Case 3

A 70-year-old man was known to have had hypertension for two years. He occasionally complained of chest pain during the night. One day before death he was rushed to hospital, after collapsing at home. The electrocardiogram revealed recent anteroseptal myocardial infarction. He rapidly developed signs of cardiogenic shock. Anticoagulants were not administered. He died suddenly one day after admission.

The necropsy confirmed the presence of a recent transmural anteroseptal myocardial infarct with rupture and tamponade (Fig. 3A). The amount of blood in the pericardial cavity was 300 ml. The myocardium at the site of rupture showed extreme thinning, with loss of necrotic muscle and adherent thrombosis (Fig. 3A and B). The rupture had occurred through a moderately thinned area. The heart exhibited one-vessel disease, restricted to the anterior descending artery. The vessel showed a recent total occlusion in its proximal segment. The aortic valve was slightly calcified, complicating a congenitally bicuspid valve. The left ventricle was very hypertrophic.

Microscopical studies of the myocardium showed a massive infiltration with polymorphonuclear leucocytes, indicative of myocardial infarction of more than one day's duration (Fig. 3C). Based upon the microscopical studies the 'age' of the infarct was estimated as between 3 and 7 days. The morphological aspects, therefore, suggest that this was another example of concealed rupture. The sudden clinical onset probably represented the onset of rupture in the setting of an unrecognized infarction.

### Case 4

A 54-year-old man suddenly developed chest pain accompanied by nausea and sweating 5 days before death. The pain disappeared spontaneously one day later. Three days later, that is one day before death, he suddenly collapsed while shaving. On immediate admission he had signs of cardiogenic shock. The electrocardiogram showed acute postero-infero- and lateral wall infarction. He was given anticoagulants. One day after admission he developed signs of mitral regurgitation, and four hours later he suddenly perished.

The necropsy confirmed the diagnosis of a large transmural posteroinferior wall infarct extending into the lateral wall of the left ventricle (Fig. 4A). A rupture in the posterior free wall had occurred, resulting in a tamponade of 400 ml blood. In addition to the free wall rupture, a partial rupture of the posteromedial papillary muscle group was present (Fig. 4A). The latter could account for the sudden onset of signs of mitral regurgitation. Examination of the coronary arteries showed one-vessel disease, with a recent complete occlusion distally in the dominant right coronary artery. There were no signs of previous myocardial infarction. Microscopical studies of the infarct revealed a massive leucocytic infiltration of approximately 3 to 7 days. It was concluded, therefore, that the sudden onset of chest pain 1 day before death probably represented the onset of rupture. It could well be that the period of chest pain experienced 5 days before death and which spontaneously subsided was the moment of onset of infarction.

## Discussion

It has been suggested by Lautsch and Lanks (1967), from a morphological study of heart rupture cases, that features often existed indicating a delayed rupture. These authors concluded, from their correlation between morphological studies and clinical histories, that in some instances the onset of symptoms could have been caused by the onset of rupture. Van Tassel and Edwards (1972), in a recent study of 28 hearts from patients with a free wall rupture, also found evidence to support this concept. Recently the term 'concealed rupture' has been proposed for this phenomenon (Becker and van Mantgem, 1975).

The term is intended for cases where the actual onset of rupture is clinically 'concealed' and interpreted as the onset of infarction. The term is proposed to contrast the common situation in which the dramatic episode of rupture, though unpredicted, is well recognized within the setting of an acute infarction. The observations described here have in common that in each of the 4 instances evidence existed for 'concealed rupture'. This conclusion is based upon a series of considerations.

Firstly, histological examination of the infarcted myocardium shows a pronounced difference in the age of myocardial necrosis. It is, of course, appreciated that an exact time-table of the reparative

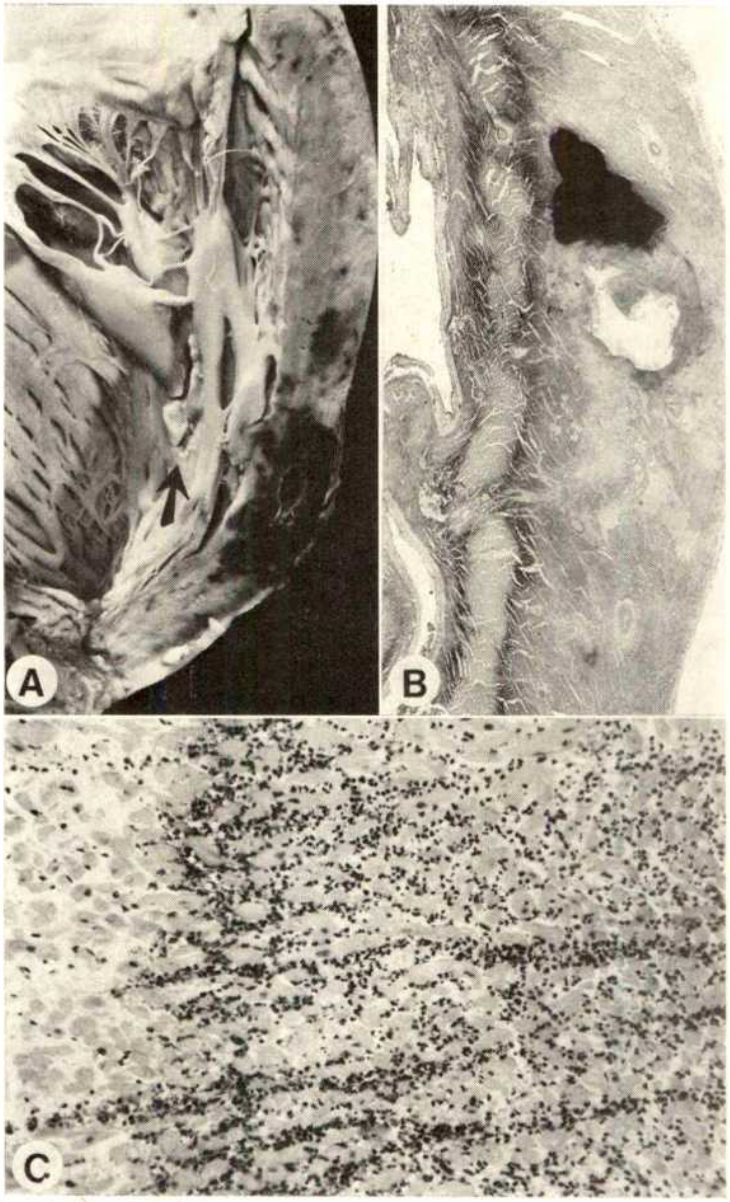

FIG. 4 *Case 4. The clinical dating of the infarct was approximately 1 day. (A) Gross aspect of opened left ventricle. The cut surface shows a haemorrhage secondary to the rupture. There was a posteroinferior wall infarct extending into the lateral wall. A partial rupture of the posteromedial papillary muscle group has occurred (arrow). The actual breakthrough is posteriorly and cannot be recognized in this view. (B) Distinct demarcation of dead myocardium by a zone of polymorphonuclear leucocytes. A recent haemorrhage related to the rupture is present in the outer part of the left ventricular wall. (C) A detailed view of a representative microscopical section. The infarct shows massive infiltration with polymorphonuclear leucocytes, indicative of an injury older than 1 day. This lends support to the view that the sudden onset of chest pain one day before death could represent the onset of rupture. (Haematoxylin and eosin. B × 4·6, C × 95.)*

responses upon infarction cannot be given. However, it is widely agreed that the invasion of the myocardium by polymorphonuclear leucocytes needs time to evolve. The classical studies of Mallory, White, and Salcedo-Salgar (1939) have shown that the earliest invasion with leucocytes can be expected approximately 24 hours after the onset of infarction. Personal experiences are in agreement with this statement. Therefore, the findings in Cases 1, 3, and 4 are considered to be of significance. In each of these instances the microscopical studies showed massive infiltration with leucocytes, which were also present in the deeper parts of the affected myocardium. Since the peak of leucocytic infiltration is generally thought to occur somewhere between 3 and 7 days after the onset of infarction, the myocardial necrosis in the 3 patients is considered to be of an older 'age' than the clinical history suggests. The same holds true for Case 2 in whom the infarction was clinically considered to be 4 days old, whereas the histology showed early fibroblastic and capillary proliferation. The cellular reaction, i.e. macrophages carrying lipofuchsin and iron pigments, was also in keeping with a reparative response of approximately 1 to 3 weeks.

The second argument is based upon the gross aspect of the actual rupture site. In each of the four instances the site of rupture showed a distinct erosion of the necrotic myocardium. It has been shown that this type of rupture coincides with myocardial infarction of a somewhat longer standing (Becker and van Mantgem, 1975).

Apparently, the 'erosion' needs time, though examples are present where the phenomenon of erosion had occurred in about 24 hours. It is an indication, however, that the tear leading to tamponade is not necessarily a sudden event. Instead, the 'erosion' in our opinion indicates that a considerable time lapse may exist between the onset of the tear and the actual epicardial breakthrough. This endorses the opinion previously expressed by morphologists (Lautsch and Lanks, 1967; Van Tassel and Edwards, 1972; Becker and van Mantgem, 1975) and is in keeping with a number of clinical reports, some of which indicate the possibility of early recognition and surgical intervention (Lillehei *et al.*, 1969; Buckley *et al.*, 1971; Mundth, 1972; Löfström *et al.*, 1972; O'Rourke, 1973; Cobbs, Hatcher, and Robinson, 1973; Calick *et al.*, 1974).

A third argument is based upon the clinical history of the patients. In retrospect, each of the patients experienced symptoms which could well be attributed to the onset of infarction. For various reasons, however, these symptoms were not interpreted as such. It seems likely that each of these patients experienced an infarct, with only minimal or non-specific signs, for some time before admission. Indeed, the high frequency of undiagnosed or clinically 'silent' infarction among a large necropsy series has previously been emphasized (Melichar, Jedlicka, and Havlik, 1963).

What then caused the sudden onset of symptoms? The possibility of recurrent infarction should be considered. However, the postmortem studies did not support this supposition. In each instance the tear went through the infarct, which itself showed the lack of correlation with the clinical history as discussed previously. The aspect of the tear, moreover, endorses the view that the process of rupturing took some considerable time. This, then, leads to the concept that the moment of sudden pain, interpreted as the onset of an infarction, represented the onset of rupture.

We are grateful to our clinical colleagues and in particular to Dr. K. I. Lie, Department of Cardiology, Wilhelmina Gasthuis, Amsterdam, for his help in evaluating the clinical records.

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# Annular subvalvular left ventricular aneurysm in Bahia, Brazil

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*Two cases of left ventricular aneurysm, a 16-year-old black boy and a 23-year-old white girl, from Bahia, Brazil, are presented. In both patients there was enlargement of the cardiac silhouette and a prominent bulge of the left inferior border. On the right oblique view a ring of calcium at the ventricular opening of the aneurysms was visualized. A left ventriculogram showed a huge aneurysm in the first case and a bulge on the lateral wall of the left ventricle in the other. Cardiac catheterization showed a rise in left and right ventricular end-diastolic pressures and in the mean pulmonary artery pressure. In the first case the contour of the right ventricular pressure curve showed a restrictive pattern. The similarities of these aneurysms with the annular submitral type described in young black Africans are stressed.*

Aneurysm of the left ventricle occurring in young people is considered to be a rare condition (Abrahams *et al.*, 1962) and has been described mainly in Nigeria, South Africa, and Uganda (Abrahams *et al.*, 1962; Chesler *et al.*, 1965; Poltera and Jones, 1973). These aneurysms are usually submitral or subaortic, the former being more frequent (Abrahams *et al.*, 1962; Cockshott *et al.*, 1967). Though the aetiology is still unknown, a congenital defect of the ventricular wall near the atrioventricular groove has been postulated as the most probable cause (Abrahams *et al.*, 1962).

In Bahia, Brazil, where other types of cardiomyopathies similar to those found in certain areas of Africa have been described (Guimarães *et al.*, 1971; Guimarães and Esteves, 1971), the two patients reported here are the first cases of annular subvalvular left ventricular aneurysm documented in life.

This report presents the haemodynamic alterations associated with this type of left ventricular aneurysm and is intended to contribute also to a better understanding of its geographical distribution.

## Case reports

### Clinical findings

**Case 1** A 16-year-old black boy was admitted to the University Hospital in February 1973, for evaluation of a tumour of the heart. Fourteen days previously he had been admitted to another hospital with acute pneumonia and then transferred to the University Hospital. At that time a chest *x*-ray film also showed a bulge at the left inferior border of the cardiac silhouette.

On admission he was asymptomatic. He referred to occasional bouts of palpitation and dyspnoea on exertion in the recent past. On physical examination the blood pressure was 110/75 mmHg (14·6/10 kPa); the radial pulse was regular and 80/min, and the body temperature 36·8°C. The neck veins were distended 2 cm above the supraclavicular fossa when the patient was reclining at 45°, and there was a prominent *a* wave in the jugular pulse. The cardiac apical impulse was palpable at the 5th left intercostal space over the midclavicular line. There was a loud third heart sound, a fourth heart sound, and a grade 3/6 diastolic murmur, louder in mid-diastole, increasing on inspiration, and audible at the apex of the heart. Some crepitant râles were present at the right lung base, and a slightly tender liver was palpable 8 cm below the xyphoid process and 6 cm below the right costal margin.

Laboratory data included a haemoglobin concentration of 11·7 g/dl, serum protein of 62 g/l (albumin 30 and globulin 32 g/l), and a negative tuberculin test with an original tuberculin concentration of 1:10·000.

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**Case 2** A 23-year-old white girl was admitted to the University Hospital in January 1975. She had a past history of episodes of fatigability, dyspnoea on exertion, cough productive of white sputum, oedema, and ascites during the past 7 years, which improved with the intermittent use of diuretics.

On physical examination the blood pressure was 120/80 mmHg (16·0/10·6 kPa); the radial pulse was 100/minute, regular and weak; axillary temperature was 36·5°C. The neck veins were distended 6 cm above the supraclavicular fossa at 45°. Crepitant râles were heard at the left lung base. The cardiac apical impulse was palpable at the 5th left intercostal space, over the midclavicular line, with a left ventricular heave; a systolic heave of the anterior chest wall was palpable at the 4th intercostal space, above the apical impulse. The second sound was widely split with an accentuated pulmonary component; a loud fourth heart sound and a grade 2/6 mid and late systolic murmur, radiating to the axilla, were heard at the apical area. The abdominal examination showed venous collateral circulation and moderate ascites; the liver was hard and palpable 6 cm below the xyphoid process and 3 cm below the right costal margin. The spleen was palpable 3 cm below the left costal margin. There was slight pedal oedema.

Laboratory data included a haemoglobin concentration of 10·0 g/dl and serum protein of 30 g/l (albumin 18 and globulin 17 g/l).

## Electrocardiogram

Both cases presented a displacement to the right of the transitional zone in the praecordial leads. In Case 1, the R wave was associated with a negative T wave in leads V2 and V3, while in Case 2 a similar abnormality was observed in leads V2 to V5 (Fig. 1 A and B). Case 1 also presented a broad P wave (0·12 s) in lead III and a ±P in V1, with a prolonged negative phase (Fig. 1 A).

## Radiological findings

On the posteroanterior chest *x*-ray film the cardiac silhouette was moderately enlarged in Case 1 and minimally enlarged in Case 2. In both cases there was a prominent bulge of the left inferior border of the cardiac shadow, the pulmonary trunk was dilated, and the pulmonary vascular markings were increased (Fig. 2 A and C) in the right middle lobe. In Case 1 there was also a triangular density at the right middle lobe of the lung. Posterior displacement of the barium filled oesophagus was noted in the right anterior oblique position, moderate in Case 1 and minimal in Case 2 (Fig. 2 B and D). In this latter view, in both cases, a ring of calcium could be visualized in an anterior position, at the base of the aneurysmal sac. In Case 2 this ring of calcium could also be visualized in the anteroposterior view (Fig. 2 C).

## Haemodynamic findings

Cardiac catheterization data are presented in the Table. In both cases there was a moderate rise in the left ventricular end-diastolic pressure, severe rise in the right ventricular end-diastolic pressure, and mild rise in the mean pulmonary artery pressure. In Case 1 the pulmonary capillary pressure showed an *x* descent of the same value as the *y* descent and the amplitude of the *v* wave was slightly above that of the *a* wave; the contour of the right ventricular pulse pressure showed a restrictive pattern (Fig. 3).

## Angiocardiography

**Case 1** The left ventricular aneurysm was outlined by the injection of contrast medium directly into its cavity: this had an irregular contour suggesting thrombus formation (Fig. 4 A). A

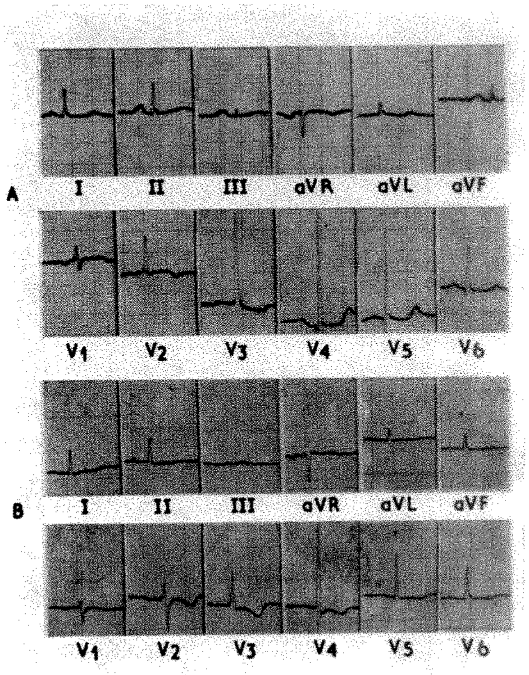


FIG. 1 *Electrocardiograms of Cases 1 (A) and 2 (B) showing displacement to the right of the transitional zone in the praecordial leads associated with primary ST T wave changes.*

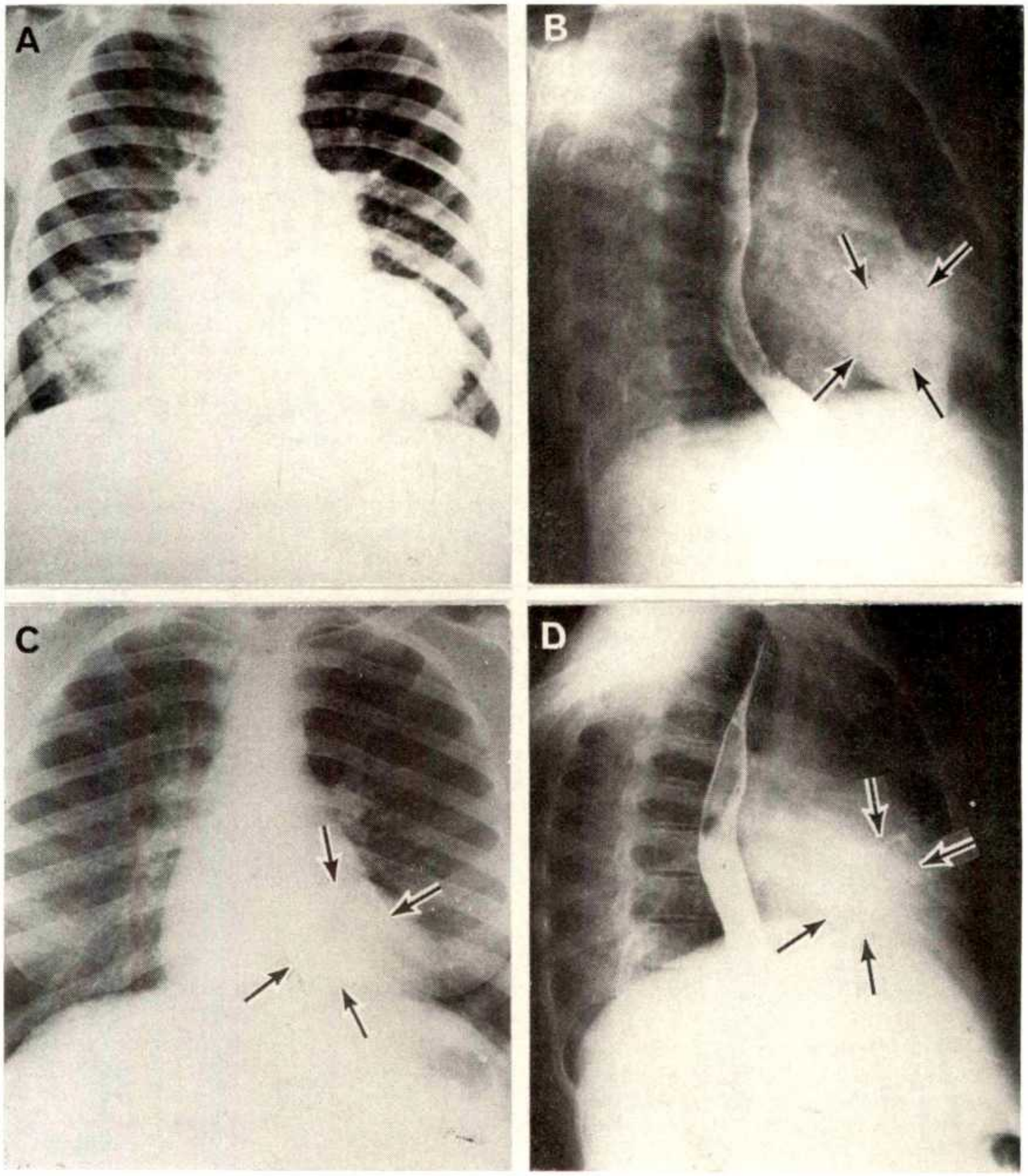


FIG. 2 *Chest x-ray films of Cases 1 (A and B) and 2 (C and D). Posteroanterior view shows enlargement of the cardiac silhouette with a prominent bulge at its left inferior border, dilatation of the pulmonary trunk, and increased vascularity of the lungs. In Case 1 (A) a triangular density is also seen at the right lower lobe of the lung; (B and D) Right anterior oblique view shows posterior displacement of the oesophagus by the left atrium and a ring of calcium (between arrows) at the opening of the aneurysms into the left ventricle. In Case 2 this ring of calcium can also be visualized in the posteroanterior view (C).*

TABLE *Cardiac catheterization data*

*Pressures (mmHg)*

| *Case* | *Right atrium* | | | | | *Right ventricle* | | | | *Pulmonary artery* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *No.* | *a* | *x* | *v* | *y* | *Mean* | *S* | $D_1$ | *Plateau* | $D_2$ | *S* | *D* | *Mean* |
| 1 | 24 | 19 | 23 | 16 | 22 | 36 | 14 | 20 | 22 | 36 | 23 | 26 |
| 2 | 22 | 13 | 18 | 9 | 17 | 43 | — | — | 18 | 32 | 18 | 25 |
| | *Pulmonary capillary* | | | | | *Left ventricle* | | | | *Aorta* | | |
| | *a* | *x* | *v* | *y* | *Mean* | *S* | $D_2$ | | | *S* | *D* | *Mean* |
| 1 | 19 | 16 | 20 | 16 | 18 | 124 | 21 | | | 123 | 85 | 106 |
| 2 | — | — | — | — | 19 | 122 | 20 | | | 122 | 78 | 98 |

S, systolic; $D_1$, initial diastolic; $D_2$, end-diastolic; D, diastolic.

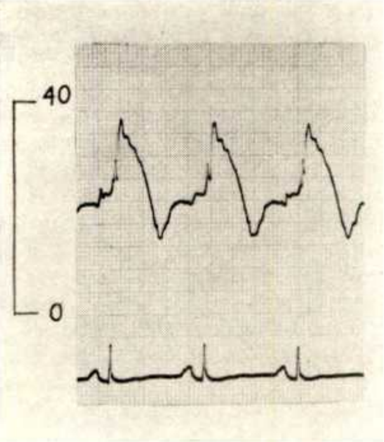


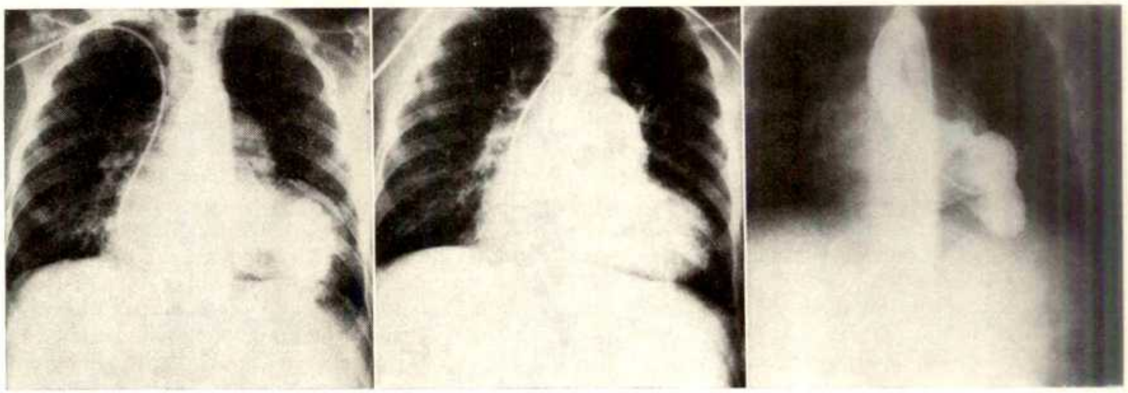
FIG. 3 *Right ventricular pressure curve (mmHg) of Case 1 shows a restrictive pattern with an early diastolic dip followed by a plateau.*

right ventriculogram showed a triangular bulge above the apex of the right ventricle (Fig. 4 B).

**Case 2** A posteroanterior left ventriculogram disclosed a prominent bulge of the lateral wall of the left ventricle, corresponding to that seen on the posteroanterior chest *x*-ray (Fig. 4 C).

### Comments

The left ventricular aneurysms reported here present all the features of the annular submitral type described in young Africans. Both our patients are from a low income social class, in which ischaemic heart disease is rarely found. In Case 1 the aneurysm was an incidental finding, while in Case 2 it was related to clinical manifestations of congestive heart failure as has been reported in the majority of the cases (Abrahams *et al.*, 1962). Physical findings in-



*A* *B* *C*

FIG. 4. *Posteroanterior angiocardiograms of Cases 1 and 2. (A) Left ventriculogram of Case 1 shows a large aneurysmal sac with an irregular contour suggestive of mural thrombus; (B) Right ventriculogram of Case 1 shows a triangular bulge above the ventricular apex; (C) Left ventriculogram of Case 2 shows a prominent bulge on the lateral wall of the ventricle.*

cluded an apical diastolic murmur in Case 1 and an apical systolic murmur in Case 2. Both types of murmurs have been previously related to blood flow through the ostia of the aneurysm (Chesler *et al.*, 1965). The systolic murmur, in addition, may be secondary to mitral insufficiency, a complication that has been frequently documented in this condition (Cockshott *et al.*, 1967). Case 1 did not present a systolic murmur, but the pulmonary capillary pressure fall suggested some degree of mitral regurgitation (Table).

The radiological diagnosis of the submitral type of left ventricular aneurysm such as is seen in our cases is based on (1) a localized bulge on the left cardiac border (Abrahams *et al.*, 1962; Chesler *et al.*, 1965; Cockshott *et al.*, 1967), and (2) calcification in the rim of the ventricular opening of the aneurysm (Abrahams *et al.*, 1962).

Retrograde left ventricular angiography is, however, the procedure of choice in investigating these aneurysms. Unfortunately we did not have facilities to perform serial angiographic studies and used a single film technique which did not allow proper evaluation of the dynamic aspects of the aneurysms or the demonstration of mitral regurgitation. In spite of these technical limitations, we were able to visualize a huge left ventricular aneurysm in Case 1 (Fig. 4 A), while in Case 2 the injection of contrast media within the left ventricle showed only a prominent bulge on its left border (Fig. 4 C). In this latter patient it was not possible to outline the whole aneurysmal sac, in spite of our impression that the injection had been made into it. Two possibilities can be considered (1) that the aneurysmal sac was partially filled with thrombus or (2) that the injection outlined only a smaller aneurysm, since in this type of aneurysm the presence of several loculi is common (Cockshott *et al.*, 1967).

The haemodynamic data documented in these two cases is interesting and deserves comment. As shown in the Table, the end-diastolic pressure in both ventricles and the main pulmonary artery pressure present similar values, as occurs in cases of restrictive heart disease (Sawyer *et al.*, 1952). In addition, the right ventricular pressure curve in Case 1 showed a restrictive pattern (Fig. 3). As shown by Cockshott *et al.* (1967), this type of left ventricular aneurysm may dissect the left ventricular wall around the mitral ring with extension to the septal myocardium leading to restriction of the filling of both ventricles, as suggested by our catheterization data. A deformity of the right ventricular septal wall is suggested by the right ventriculogram of Case 1 (Fig. 4 B). Since cases of right ventricular aneurysms have not yet been documented, the most probable explanation for such angiographic appearance is dissection of ventricular septum by the left ventricular aneurysm.

In some cases a moderate serous pericardial effusion may also be present (Williams, 1974). However, in our patients the angiographic appearance of the heart rules out this possibility (Fig. 4 A and C). Some degree of constrictive pericarditis may also occur, since the pericardium is usually thickened and adherent, obliterating the pericardial cavity.

Associated endomyocardial fibrosis occurred in one of the cases reported by Abrahams *et al.* (1962), and can be a cause of restrictive heart disease. However, in Case 1 it was ruled out by the right ventricular angiographic findings (Cockshott, 1965).

Other possible causes of cardiac aneurysms include myocardial infarction, tuberculosis, syphilis, rheumatic heart disease, collagen disorders, myocarditis, mycotic emboli, and trauma. In our cases none of these causes was apparent. The social class, age, clinical history, and electrocardiograms excluded myocardial infarction, which is the most common cause of left ventricular aneurysm. In Bahia, an endemic area of Chagas' disease, Chagas' myocarditis may be considered as a possible aetiology of cardiac aneurysms. However, the type of aneurysm seen in this chronic myocarditis is localized at the apex of the left ventricle and is small in size (Prata, Andrade, and Guimarães, 1974). Though a congenital defect of the left ventricular wall near the atrioventricular groove is difficult to prove, this may be a possible cause of these aneurysms, as proposed by Abrahams *et al.* (1962). The genetic basis suggested by the susceptibility among blacks seems unlikely, since one of the cases reported by Pocock *et al.* (1965) and one of our cases are caucasian.

Cases of annular subvalvar left ventricular aneurysm have been reported from France, Sweden, United States, South Africa, and West Indies, but the majority come from the equatorial rain forest belt of Africa, occurring in the low social income class (Abrahams *et al.*, 1962). Bahia, a northern state of Brazil, has many racial and cultural similarities with this African region, which might suggest an acquired heart disease, in which the climate and social conditions are important predisposing factors.

Both patients are under conservative management. Case 1 still maintains good functional capacity and Case 2 has compensated well after treatment for congestive heart failure. However, in spite of the high mortality figures for surgical resection of these aneurysms (Abrahams *et al.*, 1962; Chesler *et al.*, 1965; Poltera and Jones, 1973) surgery will be considered as soon as progressive deterioration takes place in either patient.

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# Pulmonary hydatid embolization
## *Report on 2 operated cases and review of published reports*

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*Two patients with pulmonary hydatid embolization are described and commented upon in the light of 43 similar published cases. The diagnosis was strongly suspected from the medical history and the chest* x-*ray films and supported by angiocardiography. The angiocardiographic features of this condition have not been described previously in detail. They include amputation and filling defects of pulmonary artery branches, which are typically located proximal to a rounded tumour-like opacity seen on the plain* x-*ray film. Both patients underwent successful embolectomy.*

Pulmonary hydatid embolization is a rare complication of cardiac or hepatic echinococcosis. A review of the world medical reports reveals only 43 cases of this condition, most of them diagnosed at necropsy (Purriel *et al.*, 1970). Only two were studied by angiocardiography and in none was a successful pulmonary embolectomy performed.

This report describes two patients with pulmonary hydatid embolization. Both underwent angiographic studies and were relieved by pulmonary embolectomy.

## Case reports

### Case 1

This 42-year-old Arab woman, born in Israel, had undergone laparotomy for removal of an hepatic hydatid cyst at the age of 22. In June 1971, she was admitted to another hospital with the chief complaints of pain in the right upper quadrant and right lower chest, cough, and shortness of breath.

On physical examination she was very breathless and there was mild cyanosis. Blood pressure was 120/80 mmHg. The pulse rate was 80/min, regular. On auscultation only a faint apical systolic murmur was heard. The right lower lung was poorly ventilated. The liver was palpated 2 to 3 cm below the right costal margin and was not tender. There was no pitting oedema of the extremities. The chest *x*-ray film showed a right-sided pleural effusion. Routine laboratory findings were normal except for the differential blood count which showed 10 per cent eosinophils. A diagnosis of pulmonary embolism was made and anticoagulant therapy instituted. Her condition improved rapidly and she was discharged in satisfactory general state. However, she was readmitted three months later with an identical picture, suggestive of recurrent pulmonary embolization. Progressive and refractory heart failure soon developed. On the eleventh day in hospital, her condition deteriorated further with increasing dyspnoea, right-sided chest pain, and a critical fall in blood pressure. The possibility of a massive pulmonary embolization was then considered and the patient transferred to the Chaim Sheba Medical Center for further evaluation and possible operation.

On admission her general condition was poor. She was in severe respiratory distress with moderate cyanosis. The heart rate was 100/min, and the blood pressure 100/70 mmHg. The neck veins were much engorged. A right ventricular heave was palpated. A grade 2/6 systolic ejection murmur was heard along the left sternal border. The second sound in the pulmonary area was widely split with a loud pulmonary component. Expiratory râles and a pleural friction rub were heard over

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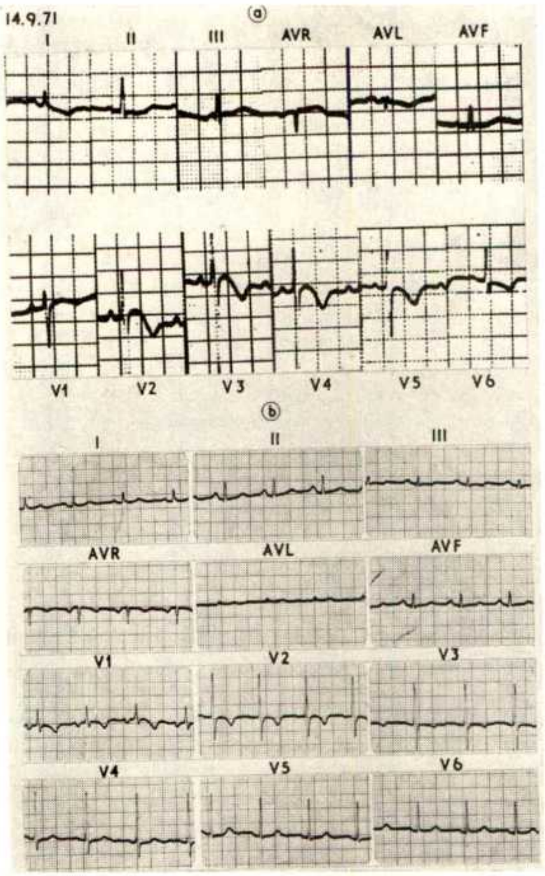

FIG. 1 *Case 1. Preoperative electrocardiogram (a) showing right ventricular overload (inverted T in V1-V6) with postoperative regression (b).*

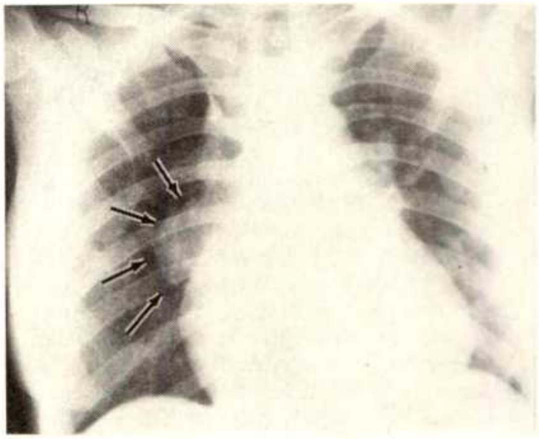

FIG. 2 *Case 1. Chest* X-*ray film, showing a round, sharply demarcated mass at the right hilum (arrows) with decreased vascularity of the right base.*

the right lung field. The liver was felt 4 fingerbreadths beneath the right costal margin and was tender. The spleen was not palpable. There was no ascites or pitting oedema of the lower extremities.

The electrocardiogram showed sinus rhythm, right axis deviation, and incomplete right bundle-branch block, with symmetrically inverted T waves in the right chest leads and clockwise rotation (Fig. 1a). The chest *x*-ray film showed moderate cardiomegaly and a rounded sharply demarcated mass at the right hilum (Fig. 2). The pulmonary vasculature of the right lower and middle lobes was decreased and a ring of calcification was seen within the liver.

These findings suggested massive pulmonary embolization. Furthermore, in view of the past history of hepatic echinococcosis and the presence of a calcified annular shadow in the liver region, the possibility of pulmonary hydatid embolization was strongly considered. An emergency right heart catheterization was then performed which disclosed a pulmonary arterial pressure of 58/30 (mean 24) mmHg, right ventricular pressure of 60/5 mmHg, and right atrial pressure of 8 mmHg (mean).

Selective injection of contrast material into the

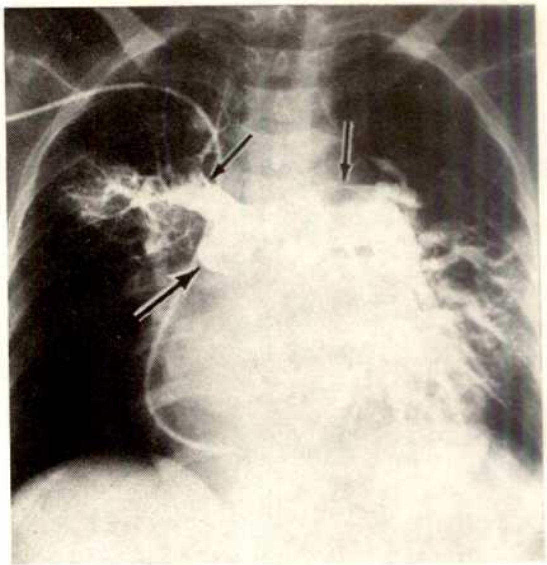

FIG. 3 *Case 1. Pulmonary angiogram, showing amputation of the intermediate branch of the right pulmonary artery (arrow head), multiple rounded filling defects in the left pulmonary artery (arrows), and amputation of the apico-posterior branches of both right and left upper lobe arteries.*

main pulmonary trunk showed that the branch supplying the right middle and lower lobes was amputated and ended abruptly with a convex stump (Fig. 3). The tumour-like mass shown on the plain chest $x$-ray film was immediately distal to this, and did not opacify. Moreover, numerous rounded, sharply delineated filling defects were seen in the opacified main left pulmonary artery and in the artery to the right upper lobe. These observations strongly supported the diagnosis of pulmonary hydatid embolization, and the patient was operated on soon after.

At operation by median sternotomy, the main pulmonary artery was seen to be dilated, and on opening the pericardium a large bulging cystic mass was seen to protrude through the right diaphragm into the pericardial space. The pericardium and the myocardium were intact with no signs of cyst rupture. Cardiopulmonary bypass was instituted and a longitudinal incision made in the main pulmonary trunk up to its bifurcation. A large number of hydatid cysts and membranes were aspirated from the left and right pulmonary arteries as far distally as possible, by suction and irrigation with saline. At the end of this procedure backflow of blood was obtained from both pulmonary arteries. The main pulmonary trunk was closed by a running suture and extracorporeal circulation stopped. The cyst which was seen to bulge into the pericardium was opened and found to be a hepatic hydatid cyst containing a large number of daughter cysts and membranes, which were evacuated. A tube drain was inserted subdiaphragmatically and the pericardial incision closed. The postoperative course was uneventful. Now, 4 years after operation the patient's condition remains satisfactory.

### Case 2

This 31-year-old man, whose case history has been reported in full previously (Deutsch *et al.*, 1969), had a hydatid cyst removed from the left ventricular myocardium in 1965. Four years later he experienced several bouts of ventricular tachycardia. A chest $x$-ray film then showed the recurrence of conspicuous bulging of the left cardiac border, and on angiocardiography a mediastinal mass compressing the superior vena cava was shown. At operation in 1969, two echinococcal cysts were evacuated from the mediastinum and a third from the left ventricular myocardium.

On follow-up examination in 1974, his clinical condition was satisfactory but a routine plain chest $x$-ray film showed a rounded, sharply delineated mass at the right hilum and decreased pulmonary vasculature of the lower half of the right lung (Fig. 4). On angiocardiography, the pulmonary artery to the right lower lobe appeared amputated and

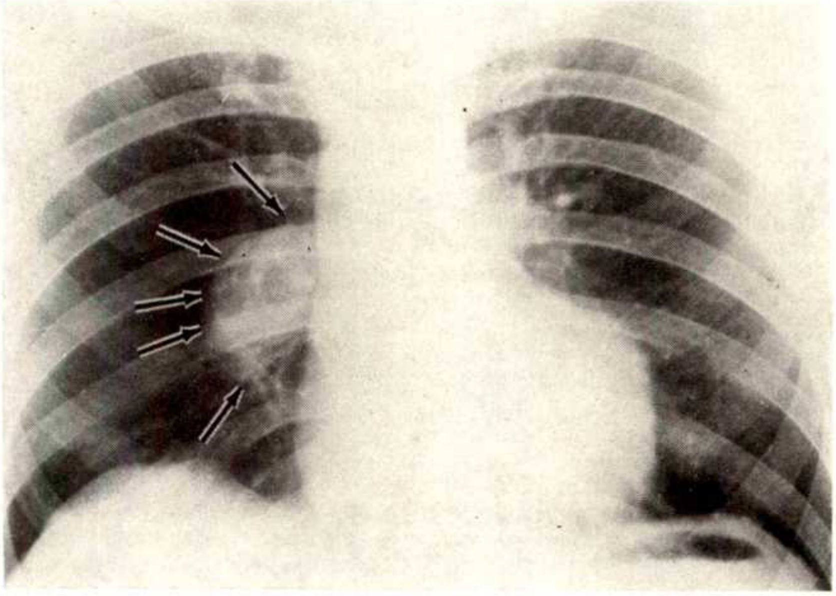

FIG. 4 *Case 2. Chest* x-*ray film, showing a large round mass at the right hilum (arrows) with decreased vascularity of the right lung. The bulging left heart border is due to a myocardial scar after cardiotomy for cardiac echinococcosis.*

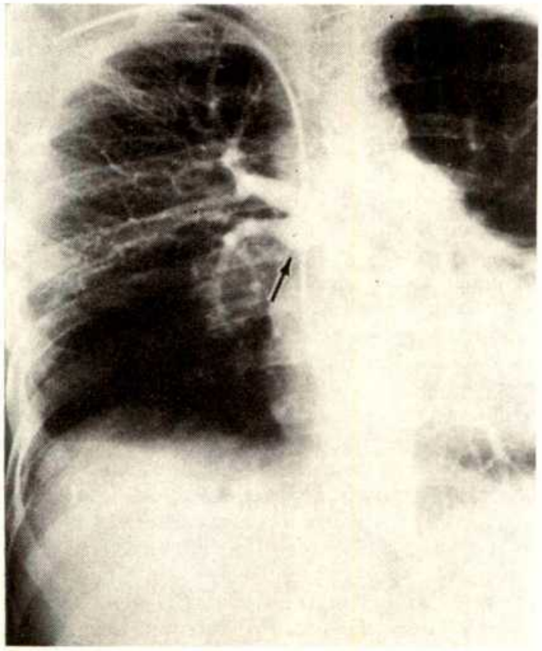

FIG. 5 *Case 2. Pulmonary angiogram. Amputation of the intermediate branch of the right pulmonary artery proximal to the hilar mass (arrow).*

ended abruptly with a convex contour. The pulmonary artery branches to the right upper and middle lobes and the left lung appeared to be normal (Fig. 5). The tumour-like mass on the plain chest *x*-ray film was seen to be distal to the occluded pulmonary artery stump and did not opacify.

From the patient's past medical history and our experience with the first case pulmonary hydatid embolization was diagnosed. At operation by right lateral thoracotomy, with division of multiple adhesions following previous operations, a large hydatid cyst, measuring 5 cm in diameter, was found at the right hilum. After the host membrane had been opened, the cyst was emptied with a trocar, and numerous daughter cysts and membranes were evacuated. Another cyst was found emerging from the intermediate part of the right pulmonary artery causing complete obstruction. On evacuation of the cyst, bleeding from the proximal part of the artery occurred and was controlled by suturing the arterial wall which was very thin and fragile. A huge hydatid cyst of the liver was then evacuated transdiaphragmatically and a drainage tube introduced below the diaphragm which was sutured.

The postoperative course was uneventful and five months later the patient remains in an excellent condition.

## Discussion

A primary hepatic or cardiac hydatid cyst is always unilocular and contains only liquid and microscopical elements, namely the brood capsules, scolices, and the products of their disintegration (Deve, 1928). When such a cyst ruptures, it rarely gives rise to mechanical complications, but subsequent growth of the disseminated fragments of the germinal layer of the hydatid cyst may result in visceral echinococcosis. Once ruptured, the cyst may degenerate, die, or give rise to daughter cysts. Pulmonary hydatid echinococcosis occurs when a cyst containing daughter cysts and membranes ruptures and empties its contents into the lesser circulation.

Intracardiac rupture occurred in 104 of the 269 cardiac cysts reviewed by di Bello and Menendez (1963). Only 27 of these presented post-mortem evidence of pulmonary hydatid echinococcosis, in 24 as a result of intracavitary rupture of a right-sided cardiac hydatid cyst and in 3 from direct rupture into the pulmonary artery. Intracavitary rupture occurred in 35 of 94 cysts located in the left ventricle (37%) compared with 30 of 34 located in the right ventricle (80%). Thus, right ventricular cysts ruptured into the ventricular cavity in a much higher percentage than those located in the left ventricle, presumably because of the much thinner ventricular wall of the former and the higher pressure within the latter.

Purriel *et al.* (1970) recently reviewed 43 reported cases of pulmonary hydatid embolization, with clinical documentation in 33, including 4 of his own. In 29, the source of hydatid embolization was a ruptured cardiac cyst and in 14, a ruptured hepatic cyst into the inferior vena cava or hepatic vein. Purriel *et al.* (1970) also showed that pulmonary hydatid embolization may occur in distal branches of the pulmonary artery. This may result in an aneurysmal dilatation of the vessel, with thinning out of its wall; eventually the cyst may break through the vessel wall and invade the bronchi or lung tissue.

Another mechanism of pulmonary hydatid embolization is erosion of a mediastinal cyst with direct penetration into one of the pulmonary arterial branches causing embolization and obstruction of the latter. This form of pulmonary hydatid embolization has been documented previously in one patient from this hospital (Kreisler *et al.*, 1965). This was a 21-year-old woman born in Iraq, who was admitted with clinical signs of severe pulmonary hypertension. A week after angiocardiography she suddenly collapsed and died in shock, death appearing to result from massive pulmonary hydatid embolization. At necropsy, the main pulmonary artery was surrounded with echinococcal cysts which compressed the artery and penetrated its wall. One of the cysts protruded into the arterial lumen. Another cyst was ruptured resulting in embolization and occlusion of the pulmonary arterial branches.

Both our cases had signs of hepatic echinococcosis. The first had no evidence of right heart echinococcosis, either at angiocardiography or at surgery. We assume, therefore, that pulmonary hydatid embolization was the result of a hepatic cyst rupturing into the hepatic veins or directly into the inferior vena cava. In the second case, the origin of the hilar cyst and of the pulmonary artery obstruction was difficult to trace at operation. A hepatic origin could not be excluded.

The clinical picture of pulmonary hydatid embolization is similar to one of ordinary pulmonary thromboembolism. In acute massive macroembolization by large echinococcal cysts and macroscopical hydatid elements, occlusion of the main pulmonary arteries may lead to acute cor pulmonale or sudden death. This occurred in 17 of the 33 cases with clinical documentation collected by Purriel *et al.* (1970). In less severe forms there may be a clinical picture of subacute cor pulmonale with raised venous pressure and decreased cardiac output. The latter was present in 3 of 33 cases mentioned above; all died within 3 to 10 months. In 13 cases, repeated rupture of a hydatid cyst resulted in recurrent pulmonary hydatid embolization. In the latter, chronic cor pulmonale developed in the form of progressive pulmonary hypertension and congestive heart failure of prolonged duration (2 to 10 years). In our first case the initial episode of hydatid embolization presumably caused only moderate obstruction of the pulmonary vasculature with a clinical picture of subacute cor pulmonale which subsided gradually. Subsequent embolizations, however, were life-threatening and necessitated prompt embolectomy. In our second case, pulmonary vascular obstruction by hydatid cysts occurred without apparent clinical manifestations.

The electrocardiogram in pulmonary hydatid embolization shows the same changes as in ordinary pulmonary thromboembolisms. Commonly there are symmetrically inverted T waves of right ventricular systolic overload in right praecordial leads (Purriel *et al.,* 1970). This was seen in our first case in whom the right ventricular strain pattern regressed after operation (Fig. 1b).

The plain chest *x*-ray appearances in pulmonary hydatid embolization which have been described recently (Purriel *et al.,* 1970) were also seen in our cases. As a result of the impaction and subsequent growth of the hydatid cysts, the affected vessels tend to display aneurysmal dilatation and tumour-like appearance, with sharply delineated borders and amputation of their branches; the corresponding lung field is oligaemic. Trapping of hydatid cysts in second or third order pulmonary arterial branches may cause local aneurysmal dilatation and the plain chest *x*-ray film may then show rounded pulmonary shadows. Cardiomegaly, with a prominent main pulmonary trunk, may also be seen.

There has been little previous experience with angiocardiography in pulmonary hydatid embolization. Purriel *et al.* (1970) briefly mentioned the angiocardiographic appearance in two cases with pulmonary hydatid embolization. They stressed only the regional changes in the pulmonary vascularity as a result of the obstruction. In both our cases the stump of the occluded main right pulmonary artery was proximal to a well-defined hilar mass. Furthermore, in our first case, multiple, rounded, polypoid filling defects were seen in the main left pulmonary artery and the branches to the apicoposterior portion of the left upper lobe. In addition, the artery to the posterior segment of the upper lobe was also occluded and ended abruptly with a concave demarcation line.

However, these angiographic features are not pathognomonic for pulmonary hydatid embolization as ordinary pulmonary thromboembolism may cause similar findings. Furthermore, hilar bronchial carcinoma or mediastinal malignant disease may also present as a hilar mass distal to an occluded pulmonary artery. Also intracavitary right ventricular tumours may propagate into the pulmonary artery and cause similar polypoid filling defects. However, in patients with a history of hydatid involvement in other organs or from endemic areas of hydatid disease, angiography can be of great diagnostic value. In these circumstances, the first clue to the diagnosis of pulmonary hydatid embolization may be seen on the plain chest *x*-ray film, as happened in both our cases. Early diagnosis, particularly in the massive form of pulmonary hydatid embolization, is of major importance because surgical intervention could be life saving.

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# Massive pulmonary arteriovenous fistula in the newborn

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*Although pulmonary arteriovenous fistula as a cause of cyanosis is well recognized, most of the reported cases occur in older children and adults, and its importance as a correctable lesion in the newborn is often overlooked. The details of two babies who presented with cyanosis in the first few days of life are presented to emphasize that this eminently treatable lesion may need to be managed as an emergency.*

Since the first description of pulmonary arteriovenous fistula (Churton, 1897), several large series have been collected (Bosher, Blake, and Byrd, 1959; Moyer, Glantz, and Brest, 1962; Dines *et al.*, 1974), and the importance of surgery to forestall paradoxical embolism, cerebral abscess, or rupture of the abnormal lung vessels, has been emphasized. Cyanosis commonly accompanies this lesion, but is not evident usually until later childhood, and most operations have been performed in adults.

The only report of a pulmonary arteriovenous fistula successfully treated in the neonatal period is that by Hall *et al.* in 1965. Reported here are 2 further cases of neonates presenting in the first few days of life with cyanosis caused by pulmonary arteriovenous fistula, showing that this lesion may need to be treated as a surgical emergency.

## Case reports

### Case 1

A normal term male infant was noticed to be centrally cyanosed some hours after delivery, and there was an easily heard systolic murmur in the right chest, loudest at the base posteriorly.

A plain chest *x*-ray film showed that the heart was enlarged, there was a rounded mass behind the lower part of the right heart shadow, and the lung fields were relatively oligaemic (Fig. 1). An electrocardiogram showed a normal axis with left ventricular dominance. The haemoglobin was 18·1 g/dl.

Cardiac catheterization showed normal pressures except for a low diastolic pressure in the pulmonary artery. Oxygen saturation of a blood sample from the left atrium was 89 per cent, from the right upper pulmonary vein 97 per cent, and from the right lower pulmonary vein 42 per cent. A pulmonary angiogram (Fig. 2) showed a dilated right pulmonary artery which filled a sac-like structure communicating directly with the left atrium.

Shortly after this investigation the baby's condition deteriorated considerably, with increasing acidosis, and an emergency operation was undertaken through a right posterolateral thoracotomy. The main pulmonary artery was encircled and controlled with a tourniquet while an attempt was made to dissect the mass, but it was found that in order to dissect it properly, the right lower lobe had to be removed. The sac was then opened and the pulmonary artery closed from within. The single vein draining from the sac into the left atrium was ligated.

He did not improve after operation and died some hours later despite all attempts at resuscitation. A postmortem study of the heart showed that there was also a patent foramen ovale and a moderate sized persistent ductus arteriosus.

### Case 2

A male baby weighing 3500 g at birth was delivered normally. Initially his condition appeared satisfactory, but 3 days later he was noted to have blue lips, and then became progressively more cyanosed though he continued to feed well and was not in any respiratory distress. On examination he

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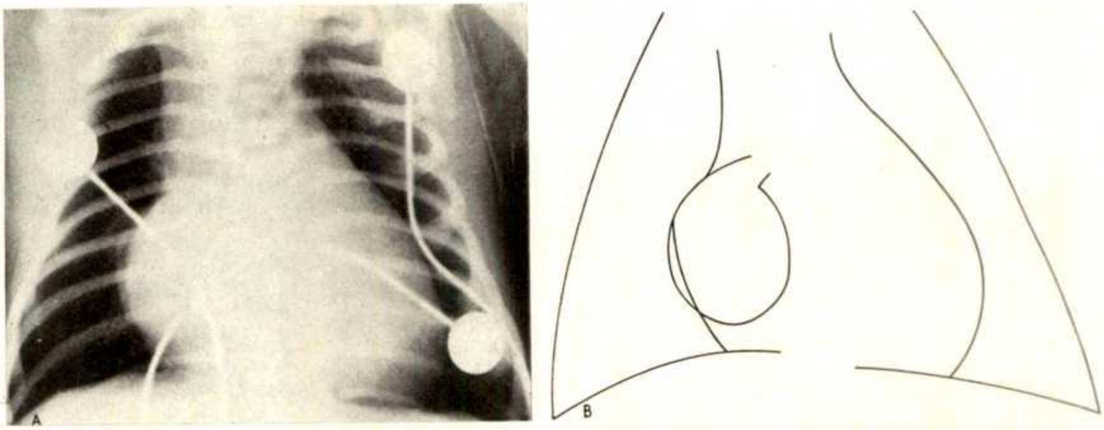

FIG. 1 *Plain chest x-ray film of Case 1 (A) showing a mass abutting the right heart shadow. This is outlined in the accompanying line drawing (B).*

was centrally cyanosed even in oxygen, and a soft systolic murmur was heard in the left infraclavicular area. A chest *x*-ray film (Fig. 3) showed a normal sized heart with oligaemic lung fields and a ribbon-like shadow in the left mid zone descending to a rounded mass in the posterior region of the left lower lobe. The electrocardiogram showed RS complexes in V1 and V4R and a dominant R wave in V6, a pattern suggestive of hypoplasia of the right ventricle. The haemoglobin was 19 g/dl, and the packed cell volume 61 per cent.

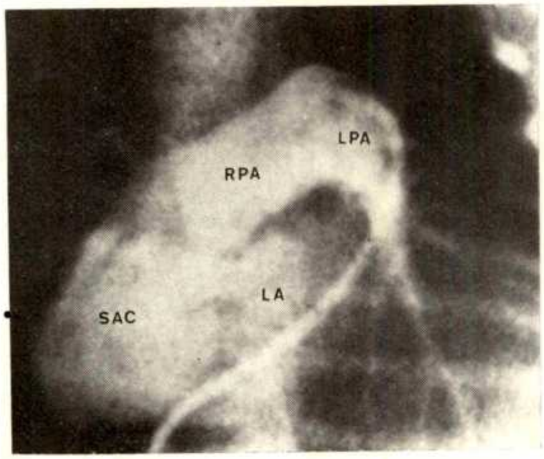

FIG. 2 *Pulmonary angiogram of Case 1 showing rapid passage of dye from the right pulmonary artery (RPA) to a sac-like structure (SAC) and then into the left atrium (LA). The left pulmonary artery (LPA) was of normal size.*

Cardiac catheterization showed normal pressures and reduced oxygen saturation of samples from the left atrium. A pulmonary angiogram (Fig. 4) showed a large dilated vessel coming off the left pulmonary artery which passed down to a saccular structure in the lower part of the left lower lobe from which dye rapidly ascended through a dilated pulmonary vein to the left atrium. The catheter also passed across a patent foramen ovale, and there was a moderate sized persistent ductus arteriosus. An echocardiogram was normal.

After our previous experience (Case 1), and because cyanosis was increasing, an operation was performed on the 4th day of life through a left posterolateral thoracotomy. A moderate sized persistent ductus was ligated and a pulsatile mass in the posterior part of the left lower lobe was seen. This was fed by a large discrete branch of the left pulmonary artery with a single large vein draining from it directly to the left atrium. These structures were ligated, but the mass remained pulsatile and was, therefore, removed by resecting the posterior basal segment of the left lung.

The postoperative course was uneventful, and he was discharged from hospital 11 days later. Pathological examination of the resected lung segment showed a large number of vessels draining into a saccular structure which was considered to be an arteriovenous malformation.

## Discussion

The majority of reported patients with pulmonary arteriovenous fistulae are adults (Moyer *et al.*, 1962), but the symptoms may develop in early

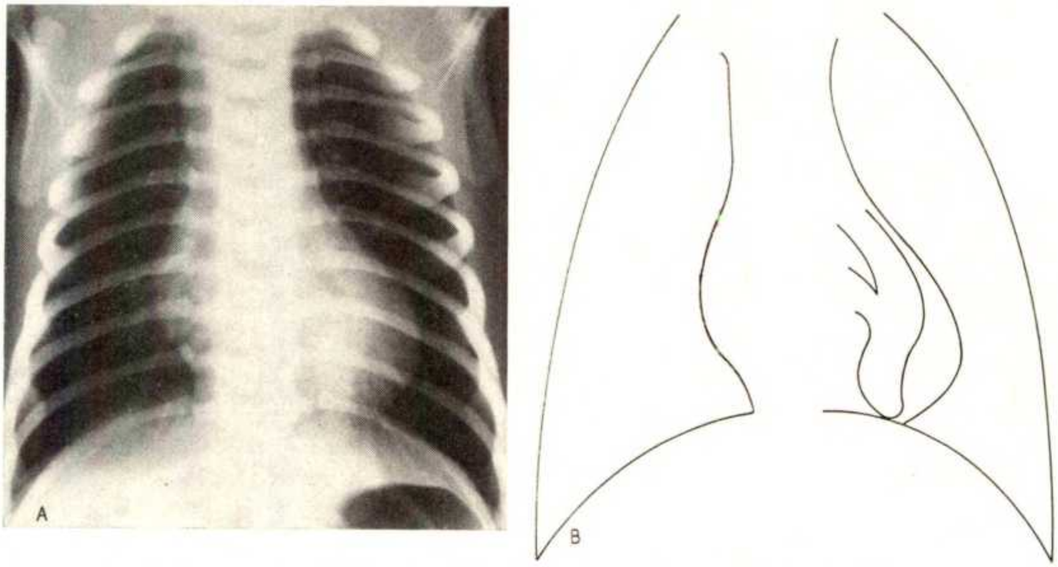

FIG. 3 *Plain chest x-ray film of Case 2 (A) showing a mass in the lower left lobe behind the heart shadow. This is detailed in the accompanying line drawing (B).*

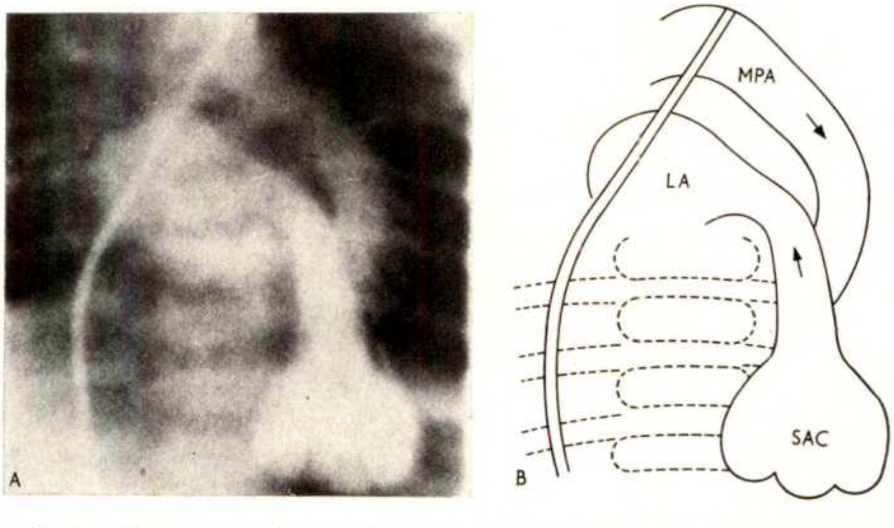

FIG. 4 *(A) Pulmonary angiogram of Case 2 showing a rounded mass in the left lower lobe filling from the pulmonary artery and draining from a separate vein to the left atrium. This is illustrated in the accompanying line drawing (B).*

life and in many cases appear to have been overlooked in infancy and childhood (Jeresaty, Knight, and Hart, 1966). Characteristically these patients are noted to be mildly cyanosed in childhood, and become increasingly cyanosed and clubbed as they grow older. While the physical examination may suggest a cardiac lesion, the malformation is often easily seen on a plain chest *x*-ray film, and can be precisely diagnosed by angiographic methods. Between a third and a half of all cases are associated with hereditary telangiectasia which is more common amongst those with multiple fistulae than single. The few cases treated in childhood have been well reviewed by Shumaker and Waldhausen (1963) and by Jeresaty *et al.* (1966), who advocate early excision of the lesion even if asymptomatic, to forestall complications such as emboli, brain abscess, and haemorrhage. The case reported by Hall *et al.* (1965) and the two reported here underline the point that this anomaly may need to be treated as an emergency when it presents in the neonatal period. A patient similar to our first case has been reported by Lucas, Lund, and Edwards (1961). He presented with cyanosis when aged 1, and died of a cerebral abscess 2 years later. Necropsy showed an almost direct communication between the right pulmonary artery and the left atrium via an aneurysmal sac.

Pulmonary arteriovenous fistulae do not usually cause an increase in cardiac output, and the right heart pressures are normal (Moyer *et al.*, 1962). Cyanosis results from a significant shunt of blood through the low pressure fistula in preference to the pulmonary parenchyma, and implies a major lesion. As Hall *et al.* (1965) pointed out, when the low resistance pulmonary bypass has existed throughout intrauterine life counteracting the effects of the normal high fetal pulmonary vascular resistance, an unusual volume load is imposed on the left ventricle. This is increased if after birth the ductus arteriosus remains patent, as was the case in our two patients.

Although the combination of central cyanosis, oligaemic lung fields, and electrocardiographic evidence of left ventricular preponderance suggests a diagnosis of tricuspid atresia or hypoplastic right ventricle, an echocardiogram will rule out these possible diagnoses by showing a normal right ventricle. Careful review of the plain chest *x*-ray film may show the intrapulmonary opacity, and allow the true diagnosis to be made.

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# Muscle potentials simulating pacemaker malfunction

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*Interference spikes were noted on the electrocardiogram of a patient with an implanted demand pacemaker. Runaway malfunction was suspected and the generator replaced. Subsequent investigation showed that the interference originated from fasciculation in the left leg caused by underlying neuromuscular disease. Skeletal muscle potentials can produce an electrocardiographic appearance closely resembling 'runaway' pacemaker. Such abnormalities should prompt a search for occult neuromuscular disease.*

Skeletal muscle activity may be recorded on the electrocardiogram, and the resulting somatic artefact is well recognized. However, multiple discrete signals on a recording which otherwise exhibits a normal isoelectric baseline have not previously been reported. This may be because the phenomenon is very rare or because it has been thought to have no clinical relevance. We report a patient who presented with this electrocardiographic pattern. Its significance was not initially appreciated, and this resulted in an implanted pacemaker being removed because of presumed runaway malfunction.

## Case report

In May 1974 a 61-year-old man was transferred to this hospital for insertion of a permanent pacemaker system. He had presented elsewhere with a history of four blackouts during the preceding six weeks. Intermittent complete heart block had been diagnosed and temporary pacing had relieved symptoms. A Devices Demand Unit (3821RC), for right ventricular endocardial stimulation, was implanted in the left pectoral region. Diabetes mellitus and hypertension, diagnosed 20 years previously, were controlled with metformin 1 g 8-hourly and methyldopa 250 mg 6-hourly, respectively. At outpatient attendance one month later he was pacing well, with no recurrence of syncope. Three months later he returned with a five-week history of palpitations accompanied by dizziness and dyspnoea. The electrocardiogram showed sinus rhythm with right bundle-branch block and left axis deviation and sharp discrete signals at a rate of 300/min in leads II and III (Fig. 1). Clinical examination revealed no abnormality in the abdomen, cardiovascular, or respiratory systems. The demand pacemaker was activated by a magnet into a fast fixed rate mode and normal pacing was evident. Analysis

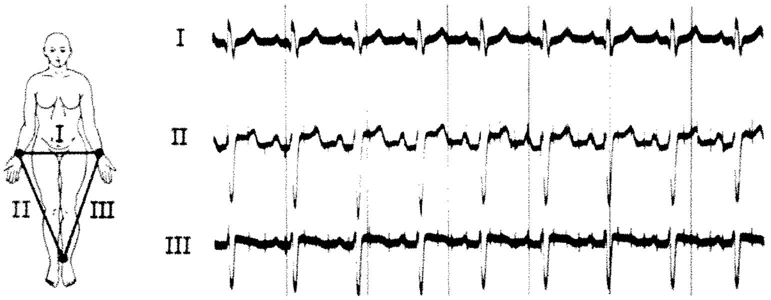

FIG. 1 *Normal lead arrangement. Presumed inhibition of demand pacemaker by return of sinus rhythm. Artefact seen in leads II and III.*

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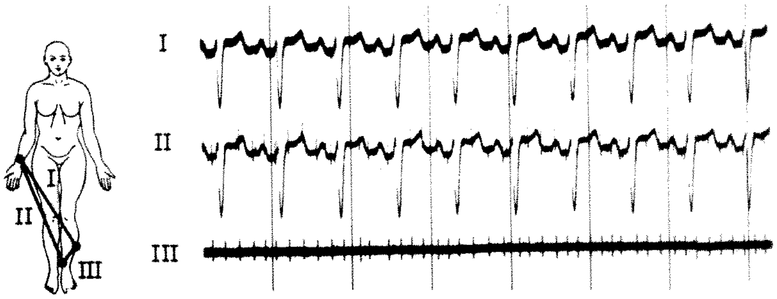

FIG. 2 *Modified lead arrangement. Leads I and II now identical, but artefact seen only in II. Artefact clearly seen on lead III.*

of the pacing stimuli showed no abnormality. Runaway pacemaker malfunction was considered because of the recent history of palpitations and the abnormal potentials on the electrocardiogram, which resembled those in an established case reported by Harper *et al.* (1974). The manufacturers thought that the normal wave form analysis and response to the magnet made pacemaker malfunction unlikely but, in view of the apparent absence of any other source of interference, urgent removal was advised, and the pacemaker generator was replaced. There was no evidence of a fault in the pacemaker.

Electrocardiographic monitoring showed no interference for the first 12 hours, but subsequently it returned intermittently. Further clinical observation revealed slight generalized muscle wasting and spontaneous fasciculations in the left calf and thigh muscles. Fasciculations could be provoked elsewhere, to a lesser extent, by exercise and percussion. On moving the left leg electrode to different areas on that limb it became obvious that the occurrence of abnormal spikes was related to electrode position. When the left arm electrode was transferred to the outer surface of the left leg (Fig. 2) the modified lead I showed a similar QRS configuration to that of lead II but without interference. In this position the modified lead III represented an axis across the left leg and showed the interference without recording cardiac electrical events. A concentric needle electrode was inserted beneath the original left leg electrode. The electromyogram from this site recorded spontaneous fasciculation potentials synchronous with each spike of interference on the electrocardiogram. Other electromyogram abnormalities found in the patient's muscles were fibrillation potentials, positive sharp waves, diminished recruitment pattern, and giant polyphasic potentials. An anterior horn cell cause for his denervation was proposed. He also had a mild peripheral sensory disturbance which was judged to be the result of long-standing diabetes mellitus.

## Discussion

Component failure may result in rapid discharge of pacemaker stimuli. The reduced amplitude of these stimuli usually results in loss of pacing but induced rates up to 300/minute have been reported (Wallace, Abelmann, and Norman, 1970). Occasionally the phenomenon is intermittent and abnormal pacemaker activity may disappear transiently (Aldridge and Kahn, 1965; Harper *et al.*, 1974). With improved pacemakers, however, this is now rare. We have not experienced such difficulties with the implanted units used at this centre (Devices Implants). The history of attacks of palpitations together with the electrocardiographic appearance led us to suspect and act on the diagnosis of runaway pacemaker in our patient. In retrospect, the fact that the abnormal potentials were seen only in electrocardiographic leads from the left leg should have made us inspect that limb more closely. As it was, fasciculations had not been observed, and we were then unaware that they could produce spikes on the electrocardiogram mimicking those from a runaway pacemaker. It is clearly important to appreciate that discrete fasciculation potentials from muscle underlying an electrode may produce interference spikes on the electrocardiogram which, in patients with an implanted pacemaker, may be misinterpreted as malfunction. Furthermore, when these spikes are seen on a routine electrocardiogram the presence of neuromuscular disease should be suspected.

We thank Dr. R. E. Nagle for letting us study his patient, and Mr. P. I. Dawes, Devices Limited, Implants Division, Welwyn Garden City, for his assistance and advice.

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# Electrocardiographic changes produced by interventricular septal rupture

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*The electrocardiogram was recorded during spontaneous rupture of the interventricular septum in a patient after myocardial infarction. The electrocardiographic abnormalities included an increase in the sinus rate, elevation of the ST segment, decrease in Q wave size, and increase in the height and width of the P wave.*

Significant areas of necrosis are found in the interventricular septum of 60 per cent of patients dying from acute myocardial infarction (Osher and Wolff 1952). However, rupture of the septum occurs in only 1 per cent of infarct deaths (Griffith, Hegde, and Oblath, 1961). Though the electrocardiographic features of septal infarction are well recognized (Osher and Wolff, 1952), we have found only one report of electrocardiographic changes recorded at the time of septal rupture (Normand *et al.*, 1965). We, therefore, report details of another patient in whom the electrocardiogram was recorded at the time of septal rupture.

## Case report

The patient, a 69-year-old woman, was admitted to the coronary care unit with a 2-hour history of tight anterior chest pain. Though she was receiving treatment for mild hypertension with a thiazide diuretic, there was no previous history of ischaemic heart disease. At the time of admission her heart rate was 80/min and regular with a blood pressure of 160/100 mmHg (21.3/13·3 kPa). Basal lung crepitations and a fourth heart sound were heard, but there was no radiographic evidence of pulmonary oedema. The admission electrocardiogram showed changes in keeping with an acute posteroinferior myocardial infarction (Fig. 1).

Throughout her stay in the unit the patient was confined to bed except for use of a bedside commode. Recordings of heart rate and blood pressure were made every 4 hours. After the admission recording, the blood pressure settled within the normal range, and the clinical state remained stable, with no rhythm disturbance or advancement of cardiac failure. Thirty-eight hours after the estimated time of onset of the myocardial infarction the patient complained of sudden return of anterior chest pain. This was accompanied by the development of hypotension (systolic pressure $< 100$ mmHg (13·3 kPa) and florid signs of cardiac failure. Auscultation of the praecordium shortly after the onset of chest pain revealed a parasternal pansystolic murmur and thrill which had not previously been present. Despite intensive supportive medical measures, the patient's condition continued to deteriorate and she died 2½ hours after the return of chest pain.

### Electrocardiogram

The patient's electrocardiogram was monitored by means of a bipolar chest lead system producing a lead II configuration and observed continuously by specially trained nursing staff on a central oscilloscope. The skin electrodes were maintained in a constant position throughout the period of monitoring. A paper strip recording of the electrocardiogram could be obtained as required.

A rhythm strip obtained 6 hours before rupture (Fig. 2A), apart from atrial ectopics, showed no change from lead II of the admission electrocardiogram (Fig. 1). A record of the electrocardiogram was obtained from the moment of recurrence of chest pain and showed an immediate 3 mm rise in the ST segment in association with a decrease in Q wave size (Fig. 2B). This was followed by a pro-

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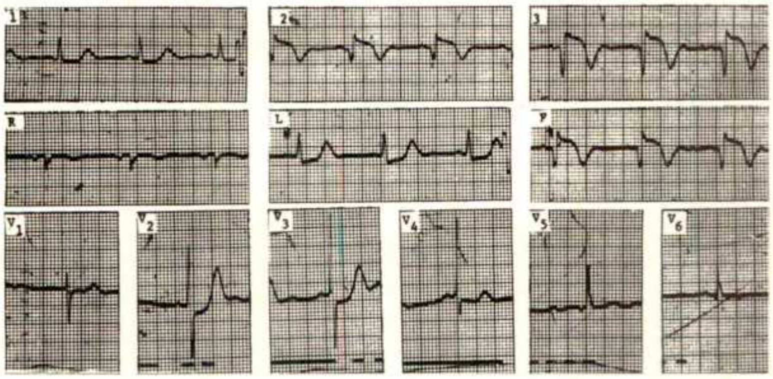

FIG. 1 *Admission electrocardiogram.*

gressive increase in the sinus rate, increase in P wave size (Fig. 2C), and runs of supraventricular tachycardia, with further elevation of the ST segment (Fig. 2D). Death occurred after the development of advanced atrioventricular block and a terminal slow idioventricular rhythm (Fig. 2E, F).

### Necropsy

Necropsy revealed a tear (5 cm × 3 cm) in the centre of a large fresh septal infarct. The right main coronary artery was totally occluded close to its origin, and though the other vessels remained patent they were heavily involved by atheromatous deposits. The pericardial sac contained a very small quantity of serosanguinous fluid.

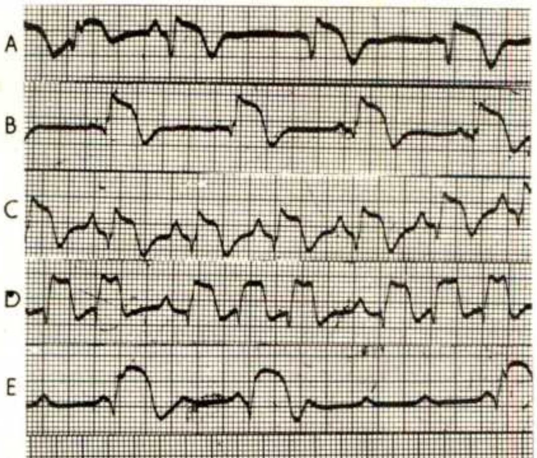

FIG. 2 *Serial monitor lead recordings.*

### Discussion

It is probable that the moment of septal rupture was heralded by the recurrence of chest pain, since it was at this point that abrupt deterioration of the haemodynamic state occurred and the parasternal murmur was first heard. Therefore, it is reasonable to suggest that the electrocardiogram, recorded during this period, relates to the rupture event.

The recurrence of chest pain was accompanied by a further rise in the ST segment, a change usually attributed to further ischaemic injury to the myocardium. A rise in the ST segment has been described in relation to rupture of the free left ventricular wall (Friedman, Kuhn, and Katz, 1971), and indeed Mir (1972) has suggested it is an indicator of impending rupture. The sudden increase in P wave size could result from right atrial strain. The appearance of such a large septal defect would produce a sizeable left-to-right interventricular shunt, with a subsequent rise in right ventricular filling pressure and a haemodynamic setting capable of producing acute right atrial strain. A similar increase in P wave size has been described by Normand *et al.* (1965) who reported two patients with interventricular septal rupture after myocardial infarction.

Although these electrocardiographic changes do seem to have occurred as a result of septal rupture, they can hardly be termed specific. We know that other complications of myocardial infarction can produce the same changes. A rise in ST segment may simply indicate the occurrence of further myocardial injury or infarction, and an increase in P wave height may result from pulmonary embolus (Wood, 1948). Likewise, rhythm disturbances and atrioventricular block are well-recognized complications in patients with myocardial infarction and and could not be attributed to septal rupture alone. Nevertheless, the changes we report, particularly

ST segment elevation followed by increase in P wave height, may add supportive evidence to a diagnosis of septal rupture occurring in the context of acute myocardial infarction.

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# Improvement in exertional left ventricular dysfunction after revascularization[1]

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*The case is reported of a 63-year-old white man with mild angina pectoris, whose systolic pressure fell 30 mmHg (4·0 kPa) with maximal exercise, without chest pain but with accompanying dizziness. Grafting the internal mammary arteries into the mid left anterior descending and obtuse marginal arteries improved regional myocardial perfusion and increased maximal cardiac output 24 per cent and maximal systolic pressure 32 per cent.*

Myocardial revascularization for ischaemic heart disease is the most common heart operation in the United States. Primarily, it is considered an operation for the treatment of angina pectoris. Reports of myocardial function before and after revascularization, however, have shown little increase in cardiac output with maximal exercise testing and a decrease in stroke volume at all levels of exercise (McDonough, Danielson, and Foster, 1974).

## Case report

This case report describes a 63-year-old white man with a two-year history of mild angina pectoris who had evidence of myocardial ischaemia with exercise, a profound fall in blood pressure with exercise (Thomson and Kelemen, 1975), and accompanying symptoms of light-headedness (Irving and Kitchin, 1975), but no chest pain. On advice from his personal physician, he participated in a jogging programme, but without improvement, and was referred to the University of Washington Division of Cardiology for evaluation. His past medical history was interesting in that he had had varicose veins removed (greater saphenous) several years before his present symptoms and his family history was positive for heart attack and stroke.

On physical examination, his blood pressure was 130/86 mmHg (17·3/11·4 kPa) and his heart rate 72 beats/min. He was in no acute distress. His neck veins were flat at 45° elevation, and his chest was clear to percussion and auscultation. His heart rhythm was regular and he had physiological splitting and an S4 gallop. Peripheral pulses were normal and equal. There was no evidence of hepatic enlargement. His legs had the scars from surgical removal of the greater saphenous veins and superficial varicosities of the lesser.

The 12-lead resting electrocardiogram was within normal limits. Chest *x*-ray showed a normal heart size; lung fields were clear.

Maximal exercise testing using the Bruce multistage protocol lasted 431 seconds (71 seconds into stage III). Blood pressure at rest was 115/70 mmHg (15·3/9·3 kPa), heart rate 65 beats/min. At maximum effort, blood pressure was 85/40 mmHg (11·3/5·3 kPa), heart rate 145 beats/min. The patient stopped with dizziness and dyspnoea. He had no chest pain. Auscultation revealed a pronounced S4 gallop. The electrocardiograph bipolar CB5 lead recorded a distinct ST segment depression of 4 mm, persisting for seven minutes.

Angiographic studies showed a 100 per cent occlusion of the proximal left anterior descending coronary artery, with retrograde filling from the right coronary artery which had multiple lesions of less than 50 per cent. There was also a tight 85 per cent stenosis proximal to the obtuse marginal artery. Left ventricular contraction was good and symmetrical. Left ventricular end-diastolic pressure was 9 mmHg (1·2 kPa) before left ventricular angiography and 12 mmHg (1·6 kPa) after injection of 50 ml contrast medium.

Because of the unusual symptoms and fall in blood pressure with exertion, the patient was evaluated with further exercise studies after giving his informed consent. A Swan-Ganz catheter was placed in the pulmonary artery and an arterial

---

[1] This study was supported in part by a grant from the National Institutes of Health, National Heart and Lung Institute, and by a grant from the National Institutes of Health.

**TABLE 1** *A. $\dot{V}o_{2\,max}$ without catheters: 2026 ml/min*

*B. Multistage test with catheters*

| *Stage/ Position* | $\dot{V}o_2$ *(ml/min)* | % $\dot{V}o_{2}$max | $A\bar{V}\,O_2$ *(ml/litre)* | $\dot{Q}$ *(litres/min)* | *HR (beats/min)* | *SV (ml)* | $\overline{BP}$ *(mmHg)* | $\overline{PA}$ *(mmHg)* | $\overline{PC}$ *(mmHg)* | *PR/ 100* |
|---|---|---|---|---|---|---|---|---|---|---|
| Supine | 284 | 14·0 | 49 | 5·80 | 67 | 87 | 86 | 19 | 17 | 58 |
| Sitting | 364 | 18·0 | 67 | 5·45 | 72 | 76 | 86 | 6 | 3 | 62 |
| Stage* ½ 3′ | 1090 | 53·8 | 110 | 9·91 | 93 | 107 | 93 | 23 | — | 86 |
| I 1′ | 1367 | 67·5 | 121 | 11·30 | 100 | 113 | 91 | 21 | — | 91 |
| II 1′ | 1632 | 80·6 | 131 | 12·46 | 120 | 101 | 91 | 21 | — | 109 |
| 2′ | 1768 | 87·3 | 146 | 12·11 | 128 | 95 | 75 | 27 | — | 96 |
| 3′ | 1895 | 93·5 | 156 | 12·15 | 134 | 91 | 63 | 29 | — | 84 |
| III 1′ | 1975 | 97·5 | 168 | 11·76 | 142 | 83 | 58 | 30 | — | 82 |
| Rec. 3-4′ | 717 | 35·4 | 103 | 6·96 | 110 | 63 | 77 | 30 | — | 85 |
| *C. Multistage repeat in 1 hour with leg wraps* | | | | | | | | | | |
| Supine | 301 | 14·4 | 56 | 5·38 | 65 | 83 | 101 | 20 | 13 | 66 |
| Sitting | 311 | 15·4 | 77 | 4·04 | 62 | 65 | 100 | 14 | 12 | 62 |
| Stage ½ 3′ | 1040 | 51·3 | 110 | 9·45 | 85 | 111 | 92 | 12 | — | 78 |
| I 3′ | 1359 | 67·1 | 130 | 10·45 | 98 | 107 | 90 | 18 | — | 88 |
| II 1′ | 1560 | 77·0 | 142 | 10·94 | 122 | 90 | 87 | 13 | — | 106 |
| 2′ | 1916 | 94·6 | 155 | 12·36 | 134 | 92 | 67 | 21 | — | 90 |
| 3′ | 1921 | 94·8 | 161 | 11·93 | 134 | 86 | 62 | 23 | — | 86 |
| III 1′ | 1968 | 97·1 | 173 | 11·38 | 149 | 79 | 45 | 29 | — | 65 |
| Rec. 3-4′ | 777 | 38·4 | 94 | 8·27 | 111 | 75 | 85 | 27 | — | 94 |

Stage* ½=1·2 mph, 0% gradient.
Stage I=1·7 mph, 10% gradient.
Stage II=2·5 mph, 12% gradient.
Stage III=3·4 mph, 14% gradient.
Stage IV=4·2 mph, 16% gradient.

*Abbreviations*: $A\bar{V}\,O_2$=difference between systolic and pulmonary artery oxygen content; $\overline{BP}$=mean systemic arterial pressure; HR=heart rate; $\overline{PA}$=mean pulmonary arterial pressure; $\overline{PC}$=mean wedge pressure; PR=systemic systolic pressure×HR; $\dot{Q}$=cardiac output, determined by Fick equation; SV=stroke volume, determined by dividing HR into $\dot{Q}$; $\dot{V}o_{2\,max}$=maximal oxygen uptake, determined from air expired during last few minutes of maximal exercise test; % $\dot{V}o_{2\,max}$=percentages of $\dot{V}o_{2\,max}$ in initial test.

*Conversion from Traditional Units to SI Units*: 1mmHg≈0·133 kPa.

**TABLE 2** *A. Six months after bypass graft surgery $\dot{V}o_{2\,max}$ without catheters:* (not attained)

*B. Multistage test with catheters*

| *Stage/ Position* | $\dot{V}o_2$ *(ml/min)* | % $\dot{V}o_2$ | $A\bar{V}o_2$ *(ml/litre)* | $\dot{Q}$ *(litres/min)* | *HR (beats/min)* | *SV (ml)* | $\overline{BP}$ *(mmHg)* | $\overline{PA}$ *(mmHg)* | $\overline{PC}$ *(mmHg)* | *PR/ 100* |
|---|---|---|---|---|---|---|---|---|---|---|
| Supine | 295 | 12·2 | 44 | 6·70 | 60 | 112 | 95 | 27 | 16 | 57 |
| Sitting | 310 | 12·7 | 59 | 5·25 | 57 | 92 | 105 | 10 | — | 60 |
| Stage ½ 3′ | 1044 | 42·9 | 108 | 9·67 | 92 | 105 | 115 | 32 | — | 110 |
| I 3′ | 1275 | 52·3 | 125 | 10·20 | 100 | — | 112 | 35 | — | 115 |
| II 1′ | — | 61·0 | — | — | 118 | — | 105 | 27 | — | 124 |
| 2′ | 1515 | 62·1 | 140 | 10·82 | 124 | 87 | 100 | 26 | — | 115 |
| 3′ | 1850 | 75·9 | 145 | 12·76 | 134 | 95 | 106 | 24 | — | 142 |
| III 1′ | 1827 | 75·0 | 147 | 12·47 | 142 | 88 | 104 | 24 | — | 148 |
| 2′ | 2199 | 90·2 | 160 | 13·74 | 150 | 92 | 98 | 25 | — | 147 |
| 3′ | 2385 | 97·9 | 163 | 14·63 | 158 | 93 | 100 | 28 | — | 160 |
| IV 1′ | 2436 | 100·0 | 166 | 14·67 | 161 | 91 | 104 | 26 | — | 167 |
| Rec. 5-6′ | 498 | 20·4 | 61 | 8·16 | 100 | 82 | 110 | 19 | — | 110 |
| *C. Percentage change between B. of Table 1 and B. of Table 2* | | | | | | | | | | |
| | +23 | — | -1·2 | +24 | +13 | +15 | +32 | -13 | — | +103 |

*Abbreviations*: (as for Table 1).

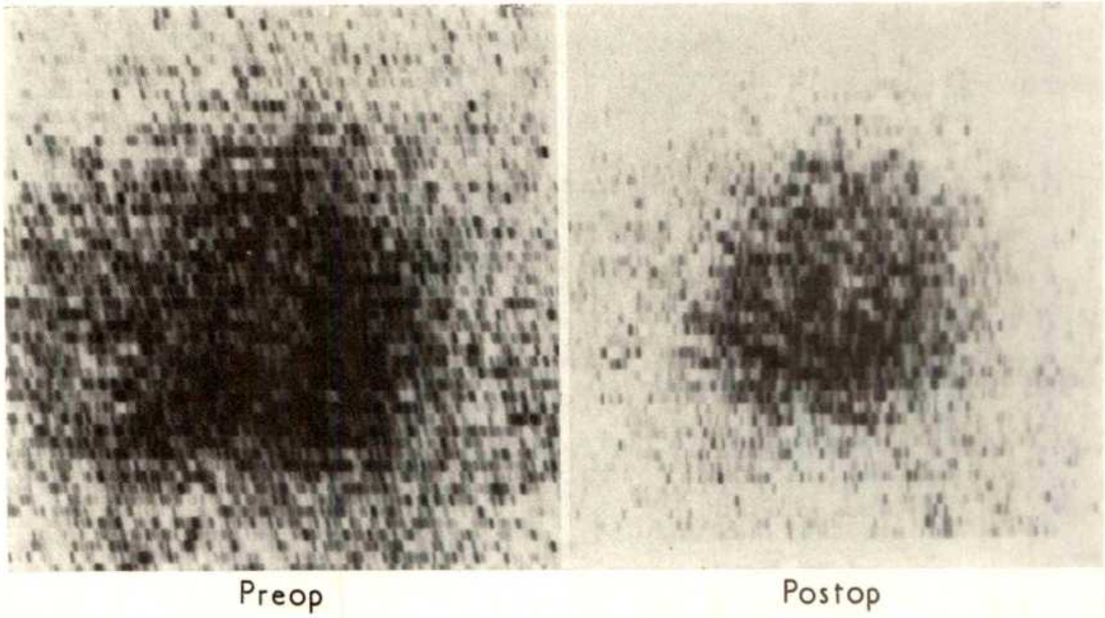

FIG. 1 *Left anterior oblique views of the myocardial* $^{81}$*Rh perfusion image recorded during independent exercise tests. Duration was identical, but the preoperative image was recorded at maximal exertion, and therefore the postoperative image was submaximal.*

catheter in the brachial artery (Seldinger technique) under local xylocaine anaesthesia. Pressure measurement and cardiac output (Fick method) were determined at rest, each stage of exercise, and during the early recovery period. The results are shown in Table 1. During the exercise test with catheters inserted, the patient was able to achieve 97·5 per cent of maximum oxygen uptake ($\dot{V}o_{2\,max}$) measured by the first exercise test (without catheters). Maximum cardiac output ($\dot{Q}_{max}$) was reached during stage II (12·45 litres/min), as was maximum stroke volume ($SV_{max}$) (113 ml). Thereafter $\dot{Q}$ and SV both fell, accompanied by a fall in mean systemic pressure to 75 mmHg (10·0 kPa) and a compensatory increase in AV $O_2$ difference. Because of his varicose veins, the exercise test was repeated after leg-wrapping to establish whether the fall in blood pressure could be explained by the abnormal venous capacitance of the remaining varicose veins. The results are shown in Table 1, and represent no appreciable improvement.

Two months later the patient had a bypass operation, grafting the internal mammary arteries to the mid left anterior descending (flow rate 55 ml/min) and obtuse marginal arteries (flow rate 25 ml/min). At operation, calcific atherosclerosis was noted in his distal right coronary and left main coronary arteries. The bypass surgery took 139 minutes and the operative procedure and postoperative period in hospital were without complications.

Six months after the operation, the patient volunteered for restudy. The results are shown in Table 2. There was a pronounced improvement in duration of the exercise test, which continued through one minute of stage IV. Maximum cardiac output was now 14·6 litres/min and stroke volume slightly lower (105 ml) than on the previous occasion. During exercise, the mean systolic pressure fell by only 10 mmHg (1·3 kPa), a distinct change from the previous tests. The patient no longer complained of light-headedness. Myocardial perfusion scanning using $^{81}$Rh before and after operation showed an obvious improvement in the perfusion of the region of the left anterior descending artery. The standardized exercise tests were of the same duration.

## Discussion

This case illustrates an unusual finding, in that the fall in systemic pressure with exercise accompanied the patient's complaint of light-headedness because cardiac output was limited by ischaemic heart disease. Resting angiographic studies showed normal left ventricular function, as did the myo-

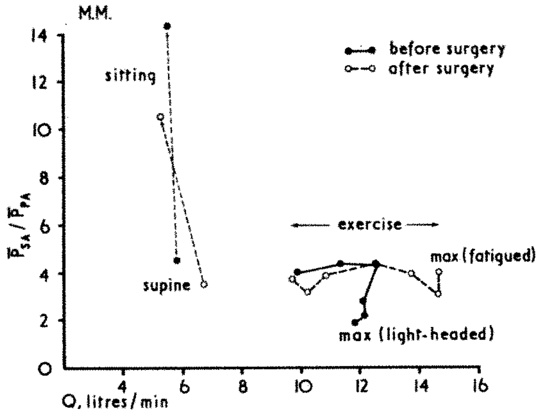

FIG. 2 *Ratio of mean systemic pressure over mean pulmonary pressure to cardiac output at rest, supine and sitting, and then at each stage of exercise. Evidence of left ventricular failure preoperatively is noted at the second minute of stage II and in the progressive fall thereafter. Postoperatively, the pressure ratio remains fairly consistent, with the continued rise in cardiac output.*

cardial perfusion scans done at rest. Myocardial revascularization brought about a definite improvement in maximal cardiac output and maximal systolic pressure, an uncommon occurrence with this procedure (Fig. 2). It suggests reversible exertional left ventricular dyskinesis. This case illustrates the benefit of adequate study with a maximal exercise testing procedure in the evaluation of ischaemic heart disease.

The authors wish to acknowledge the assistance of Dr. J. L. Petersen and Dr. L. R. Sauvage in the medical and surgical aspects of management of this patient.

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Requests for reprints to Professor R. A. Bruce, Division of Cardiology, RG-20, University of Washington, Seattle, Washington 98195, U.S.A.

# *Obituary*

*British Heart Journal,* 1976, **38,** 1105–1107.

# Sir John Parkinson

Sir John Parkinson, born in Thornton-le-Fylde, Lancashire, on 10 February 1885, died at the age of 91 on 5 June 1976. He had worked untiringly throughout the whole of his professional life to establish cardiology as an acknowledged specialty within medicine. A notable step towards this ambition took place when the Cardiac Club of 15 members was enlarged to admit 85 members in 1937, and renamed the British Cardiac Society. Parkinson became its first president in 1952. The Society now has a thriving membership of 400, while its monthly journal, the *British Heart Journal,* enjoys an international reputation. He had set his heart on achieving for cardiology this premier position in medicine, and before retiring from active practice he had the satisfaction of knowing and seeing that this had come to pass. That he acted wisely in this has been amply confirmed, since it assured for this country a safe place in the van of modern cardiology.

Parkinson received his premedical education at the Manchester Grammar School and University

College, London. He trained in medicine at the University of Freiburg and the London Hospital which he joined in 1903, and later described it as his medical home. There he gained prizes in anatomy and physiology, and the Anderson prize in clinical medicine. He graduated in 1907, and after holding junior posts, he became medical registrar in 1911. In 1913 he became first assistant to Sir James Mackenzie in the cardiac department.

In the European war he served in France, first as medical officer to a casualty clearing station, and later as major in the RAMC in charge of the Military Heart Centre at Rouen. He was divisional officer at the military hospital for heart cases at Hampstead. When Sir James Mackenzie moved to St Andrews in Scotland in 1919, Parkinson assumed charge of his department at the London Hospital, and later he became physician to the National Heart Hospital.

The excellence and constancy of his work in and for cardiology within medicine gained for Parkinson recognition, honour, and distinction from many lands. He was elected President of the Euroyean Society of Cardiology, and of the Association of Physicians of Great Britain and Ireland. He received honorary degrees from the University of Glasgow, and the National University of Ireland, and honorary fellowships from the Royal Colleges of Physicians of Edinburgh, Ireland, and Glasgow, the American College of Physicians, and the Royal Society of Medicine. He was created an honorary member of the cardiac societies of France, Italy, Switzerland, Portugal, India, Brazil, Australia, and New Zealand. He was made consulting cardiologist to the Royal Air Force in 1931. The Royal College of Physicians appointed him Lumleian lecturer and Harveian orator, and awarded him the Moxon medal, while from the Medical Society of London he received the Fothergill gold medal. He received the gold stethoscope award of the International Cardiology Foundation in 1966. In 1948 he was invested with a knighthood.

By nature, Parkinson was a shy man. He enjoyed the company of close friends when he was a generous host, but unless obligatory, he preferred not to dwell long in the company of strangers, unless those with a common interest and especially the young seeking his advice; to them he would devote unlimited time and help. He despised committees, and his attendance at any came from compulsion. To speak publicly, apart from lecturing, was not to his liking, but at such discursive meetings, should the views expressed be contrary to his own, he would rise to speak, usually briefly, and always convincingly. He could converse in both German and French. His punctuality was proverbial; never late at a consultation, lecture, ward-round, or out-patients' session.

Parkinson wrote no textbook of cardiology, but he did more, he undertook personal research into most ailments to which the heart is heir, and he conveyed his findings in his many publications. His collected papers, which are to rest in the library of the Royal College of Physicians, are literature enough for cardiology. Parkinson was no copyist. He cut his lone furrow, and those of us who viewed it from the headlands saw it as a pattern which we would wish to follow. In his researches he never allowed his gaze to stray from his avowed object of improving the diagnosis of heart disease in order to bring it within the compass of practical therapy.

Dealing first with *treatment,* he and Sir Alun Rowlands tested the effects of strychnine in heart failure at a time when it was standard therapy in patients with that condition. They found that it produced no benefit; their findings were announced at the 17th International Congress of Medicine in London in 1913. Parkinson was the first to introduce adrenaline in the treatment of Adams-Stokes attacks. In 1917 he wrote on the uselessness of digitalis in the so-called soldiers' heart, and in 1922 on the use of quinidine in paroxysmal and established auricular arrhythmia. In 1936 he highlighted the beneficial effect of a mercurial suppository, some years before the introduction of modern oral diuretics. In 1939 he and Gavey showed that digitalis was always indicated in heart failure irrespective of the heart rhythm. He warned not to accept readily statements on the superiority of new analgesics over morphine, a drug whose universal use through more than a century gave proof of its wonderful efficiency, and he reminded an audience of doctors that some of them were mean in their use of analgesics, adding that their attitude might change when they became ill themselves. To Parkinson, unfamiliar medicines were suspect, so that when I first reported to him for duty as his house physician, he warned me not to prescribe any medicine to patients admitted to hospital under his care, until he had seen and examined them. I interpreted this caution as an absence of confidence in his new house physician, but I was soon to notice how well the patients reacted to rest only, and in the absence of any medicinal therapy. Indeed, as house physician to Parkinson, I learnt that nature was itself a physician capable of curing illness, and that a knowledge of the natural history of disease along with its dictum of *vis medicatrix naturae* was being annihilated by overzealous therapeusis.

In 1925 he supervised a patient with mitral valve disease in whom Sir Henry Souttar undertook digital dilatation of the mitral ring. Parkinson had retired from active medical practice when surgical treatment of heart conditions was gaining notable success, a progress he warmly applauded.

In the *diagnosis* of heart disease Parkinson made significant advances in several sectors. Evan Bedford and he were foremost in correlating the symptoms and electrocardiographic signs of cardiac infarction (coronary thrombosis), especially identifying the changes that take place during the weeks and months which follow the initial attack. With Maurice Campbell and Bedford he wrote extensively on the arrhythmias, with Clifford Hoyle on the heart in emphysema, and with Harold Cookson on the heart in goitre. In 1930, along with Louis Wolff and Paul White in America, Parkinson described bundle-branch block associated with a short PR period in healthy young people prone to paroxysmal tachycardia (the WPW syndrome). The paper in which they discussed this anomaly has been quoted in cardiological journals with a frequency probably greater than any other. Jointly with Bedford and Papp, he wrote a comprehensive dissertation on atrial septal defect which presently led to its more frequent surgical treatment. Parkinson's greatest contribution to diagnosis came from his compulsive encouragement to view the heart radiologically. Extolling this method, he pointed out that no organ was so favourably placed for *x*-ray inspection as the heart, for it was surrounded by translucent lung, while rotation of the patient enabled the heart to be viewed from all angles. In this way we look at individual chambers of the heart separately and not just its mass.

Parkinson's wise leadership in *clinical* cardiology will be remembered as long as hearts keep beating, and an age ahead will rediscover the truths he taught so convincingly at the bedside. He had a passion for truth. He relied on facts; he was never given to imagination, for the truth to him was what he saw. Indeed, he seemed a tyrant for truth, and through his diligent search for it, he often presaged it.

He did not decry a thorough investigation of a patient's illness, and electrocardiography and cardioradiology were never omitted in uncovering concealed heart disease, or making its nature better understood, but he warned sternly against unneeded investigations in a stinging epigram: 'There is always a moment when curiosity is a sin'.

Parkinson was a plunderer for perfection. Should one of his assistants submit a film of his own recording, expecting to win high praise from the master, it was ever likely to draw a terse remark, highlighting a tiny flaw in the far corner of the film. Censure would then carry the injunction that no such exhibit should leave his department for publication. The assistant would retire subdued, but having taken a decided step towards perfection. He sought perfection too in the lay-out of his garden, addressing each shrub by its Latin name, and in the choice of furniture and paintings in his home and consulting-rooms; he himself was no mean painter in water-colour.

It is not only what John Parkinson did and said that have so materially benefited our knowledge of the heart in health and in disease, but also the way he said it. The purity of his prose in his writings and his lectures abound with examples of those apt and happy turns of phrase which fell so naturally from his pen and so authoritatively from his lips.

As we honour the passing of Sir John Parkinson we pay tribute to a great physician and cardiologist and a great teacher.

It were never possible for a man, so bent on enduring competency, to carry on while at the same time entertaining cardiologists who came from overseas to see his department and his work unless supported by a spouse of unusual composure and ability. Lady Parkinson, who predeceased her husband by two years, was such a one. Capable, tactful, self-possessed, graceful, and the epitome of calm, she was his constant help and counsellor on his climb to fame.

To the four daughters who survive their parents we extend our sympathy.

William Evans

## *Correspondence*

*British Heart Journal,* 1976, **38,** 1108.

# Imperforate Ebstein's anomaly of the tricuspid valve

Sir:

In the case report by Gerlis and Anderson (*British Heart Journal,* 1976, **38,** 108), the authors are not correct in saying that there is no previous description of imperforate Ebstein's anomaly of the tricuspid valve. In 1973, we reported a case of Ebstein's malformation of the tricuspid valve with complete obstruction to the tricuspid valve orifice, i.e. atresia (Rao *et al.,* 1973). The associated lesion was a ventricular septal defect. In this report we presented clinical, catheterization, angiographic, and pathological data of this case and discussed the differentiation of this anomaly from the usual cases of tricuspid atresia as well as the surgical implications. We also noted that Van Praagh, Ando, and Dungan (1971), Miller (1971), and Lev *et al.* (1970) had previously mentioned similar cases. Therefore, I believe that imperforate Ebstein's anomaly of the tricuspid valve is adequately described and documented.

P. Syamasundar Rao,
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Medical College of Georgia,
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### References

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Rao, P. S., Jue, K. L., Isabel-Jones, J., and Ruttenberg, H. D. (1973). Ebstein's malformation of the tricuspid valve with atresia: differentiation from isolated tricuspid atresia. *American Journal of Cardiology,* **32,** 1004.

Van Praagh, R., Ando, M., and Dungan, W. T. (1971). Anatomic types of tricuspid atresia: clinical and developmental implications (abstract). *Circulation,* **44,** Suppl. 2, 115.

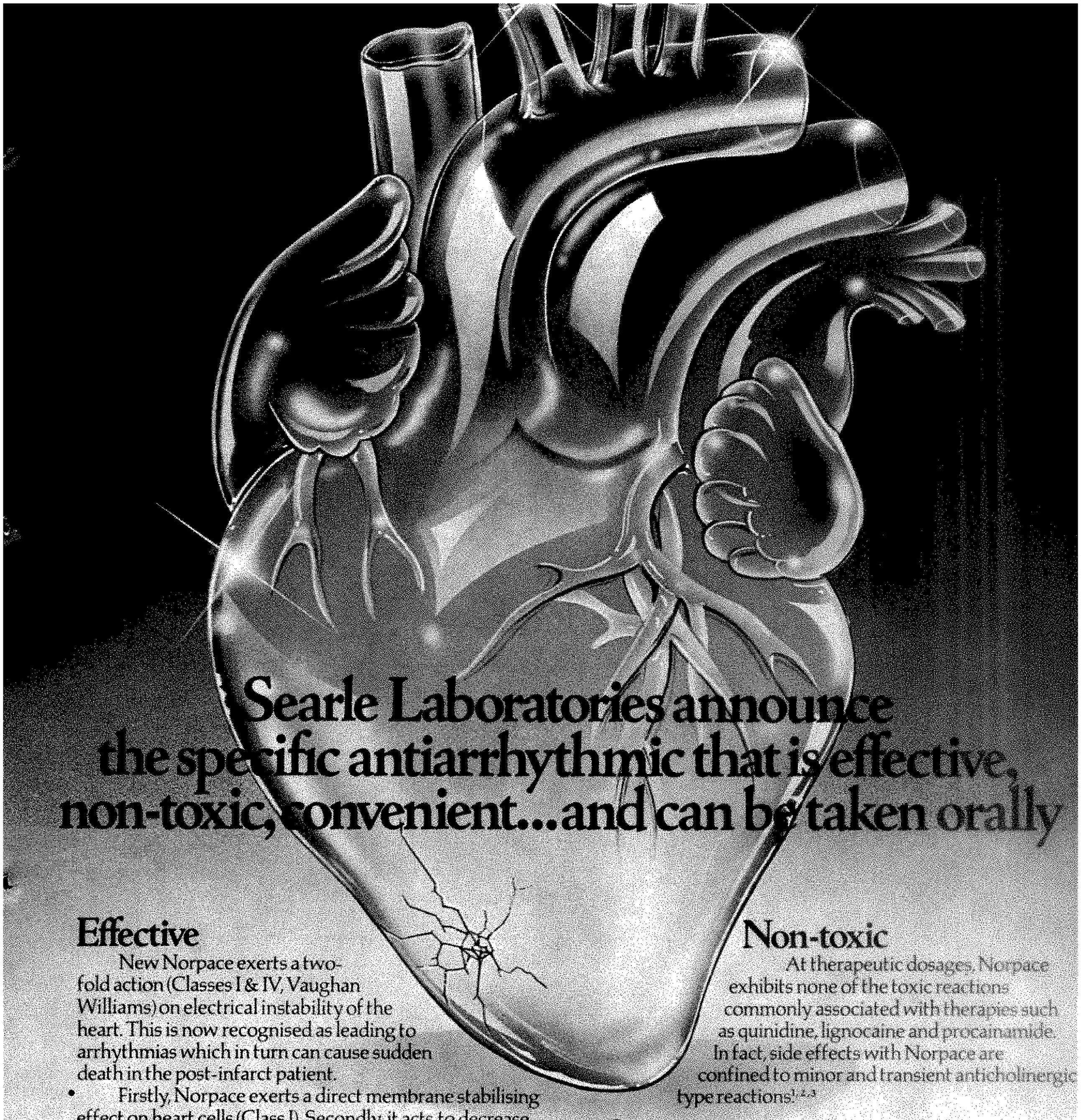
This letter was shown to the authors who reply as follows:

Sir:

We thank Dr. Rao for his comments and particularly for bringing to our attention the earlier descriptions of imperforate Ebstein's anomaly of the tricuspid valve.

He is completely correct and we regret our oversight.

L. M. Gerlis and
R. H. Anderson,
Department of Pathology,
Grimsby General Hospital,
Grimsby,
South Humberside;
and
Department of Paediatrics,
Cardiothoracic Institute,
Brompton Hospital,
Fulham Road,
London SW3 6HP.



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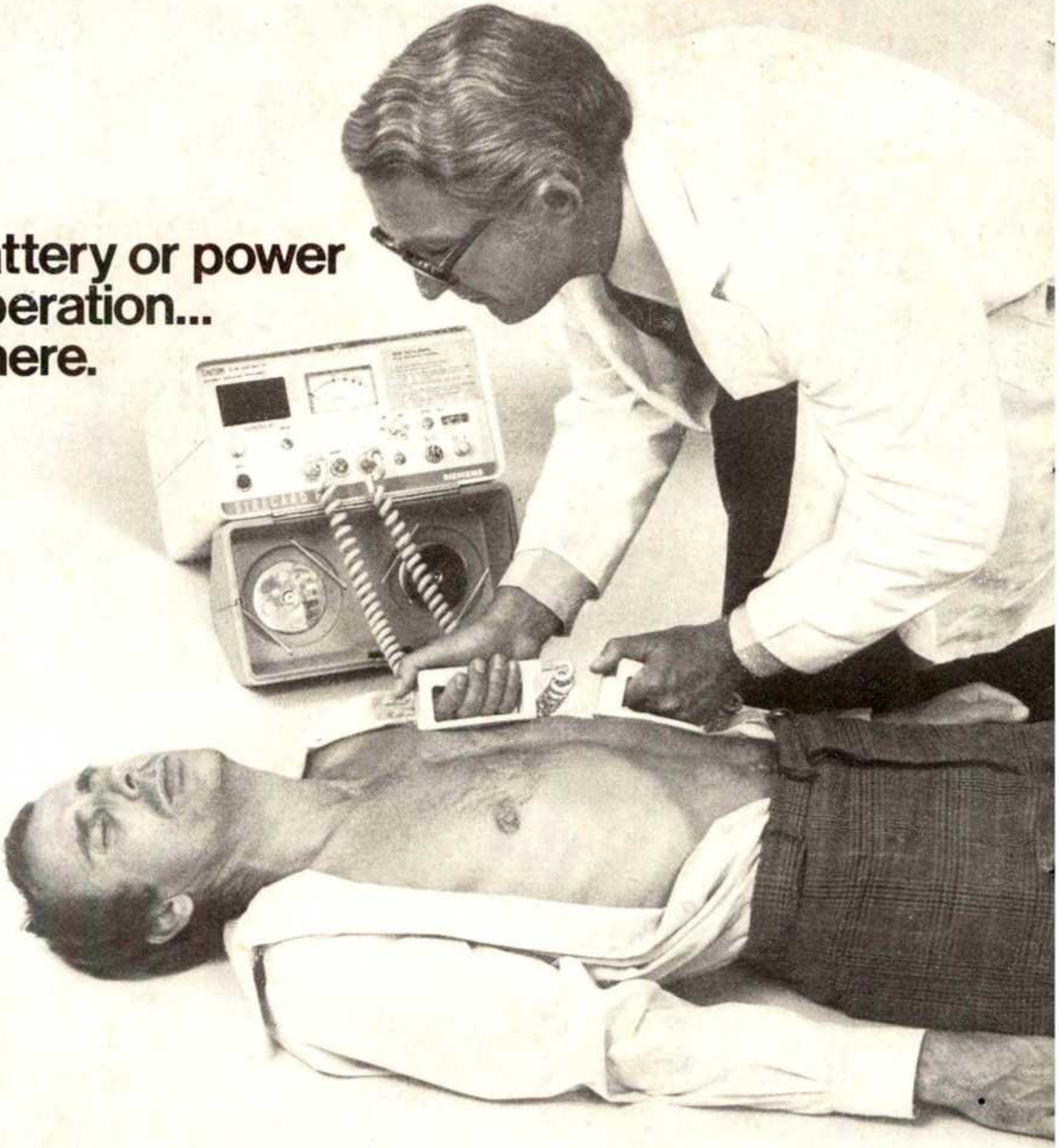

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1. Postgrad. Med. J., 51, 10, (1975)
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# British Heart Journal

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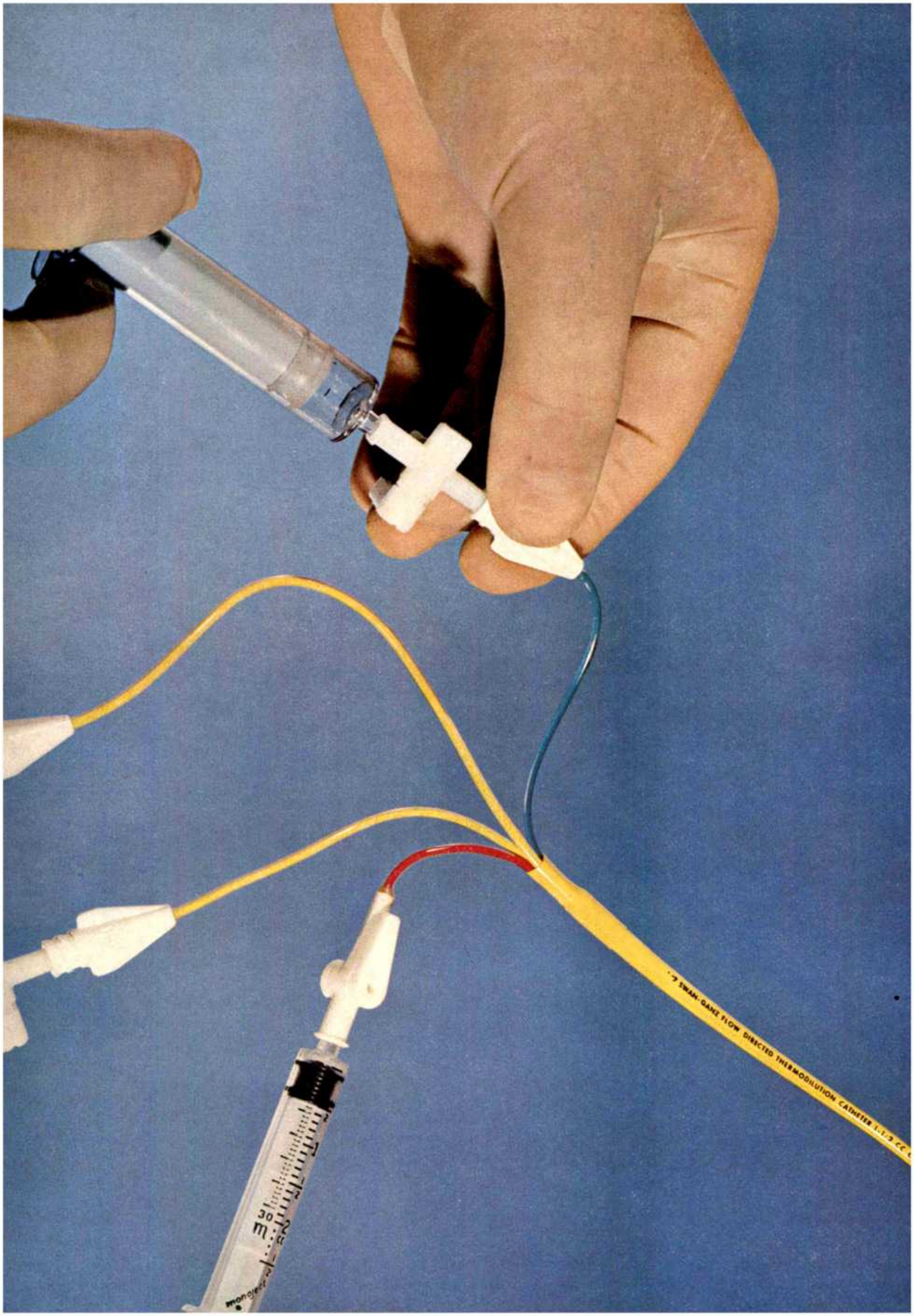
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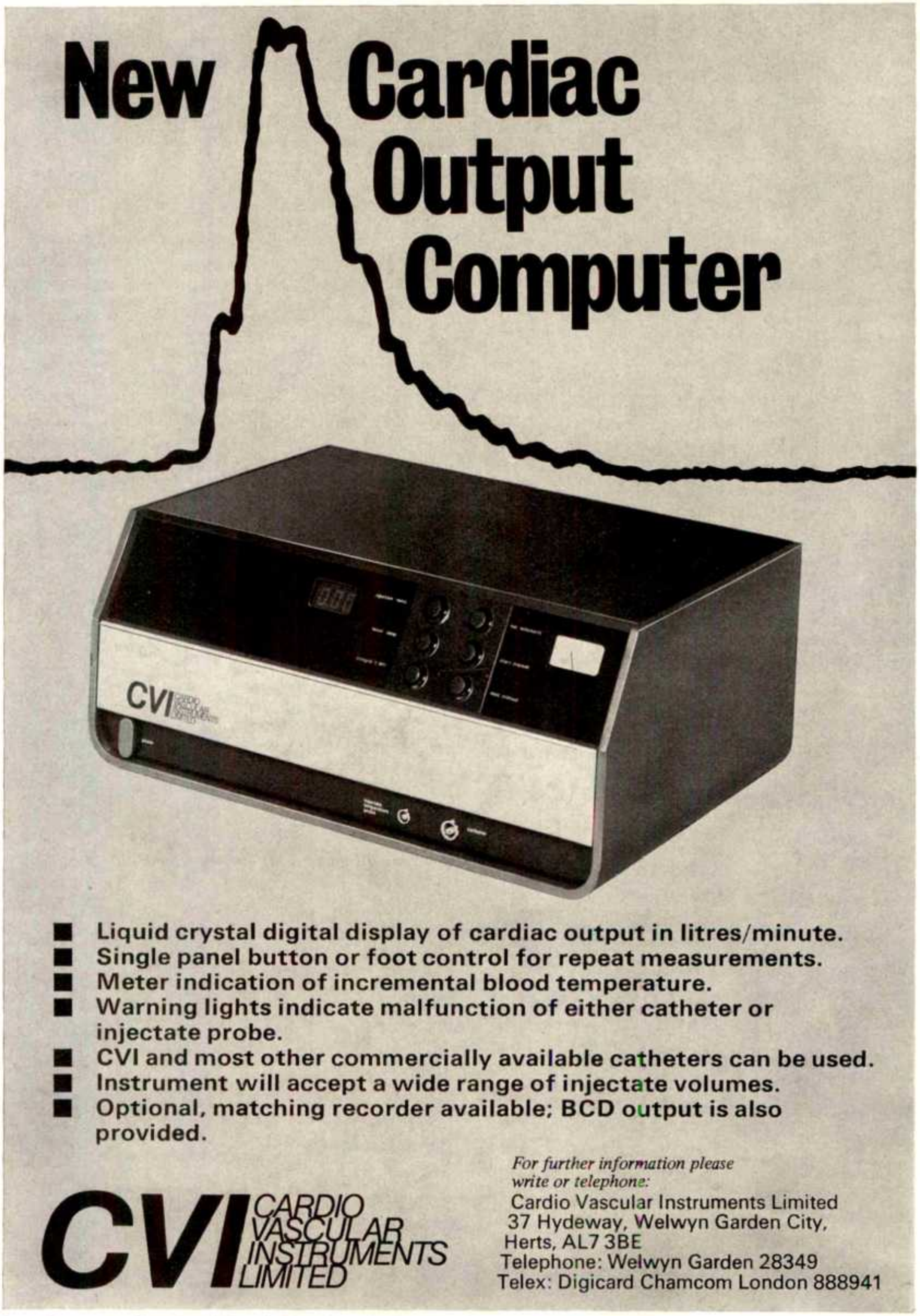

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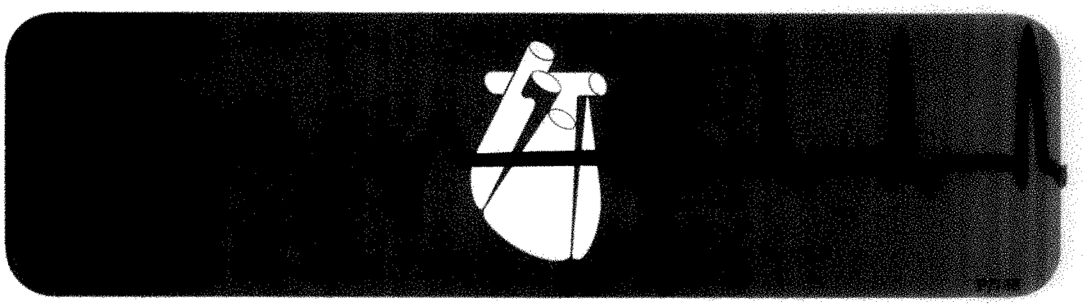

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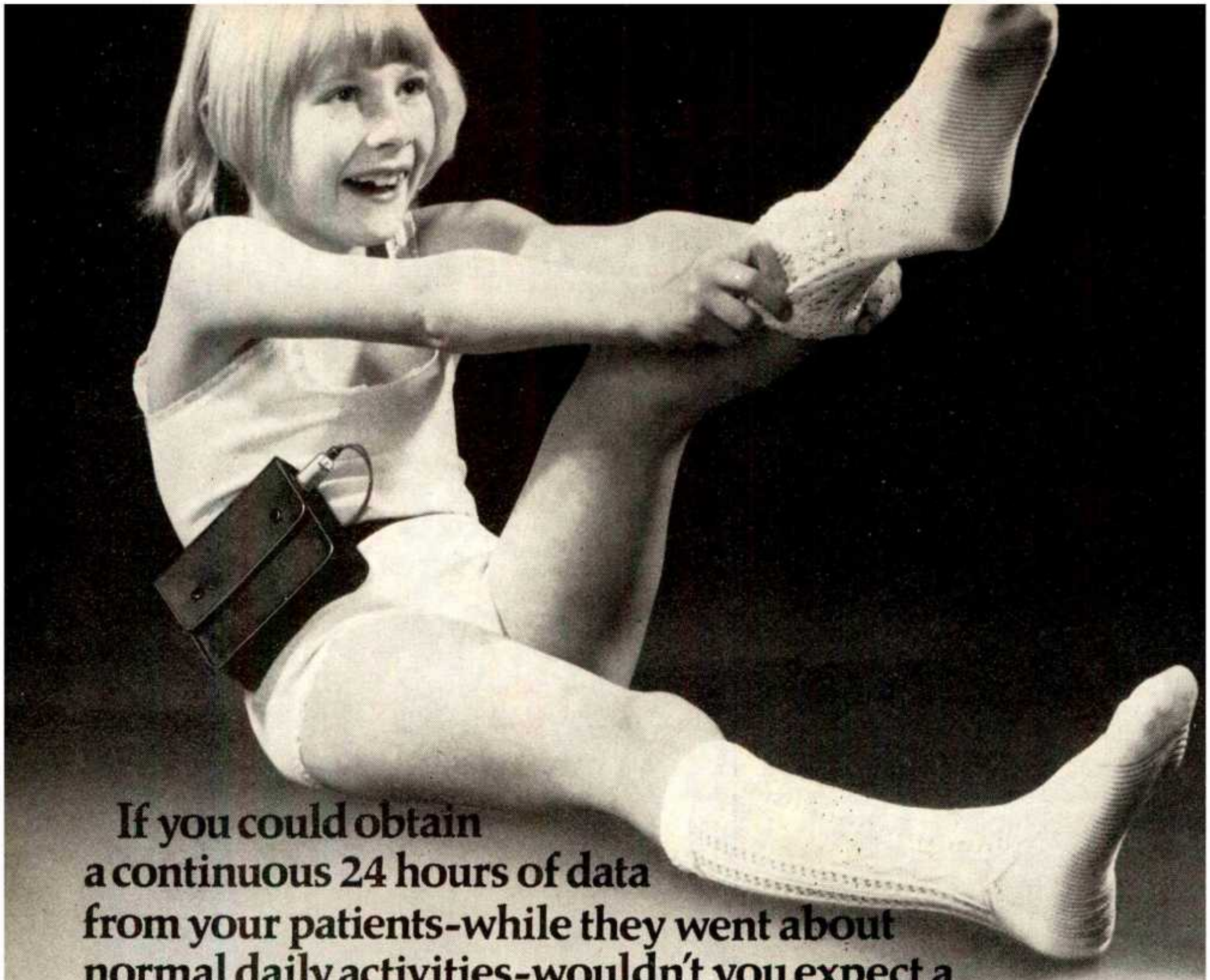

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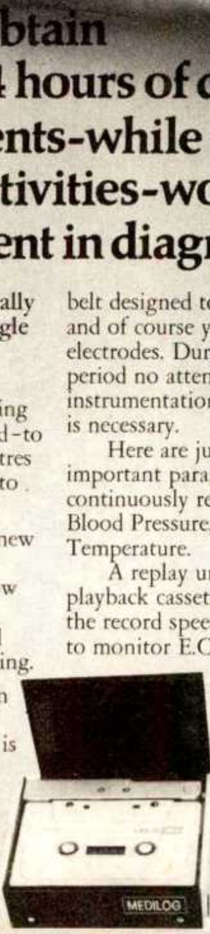

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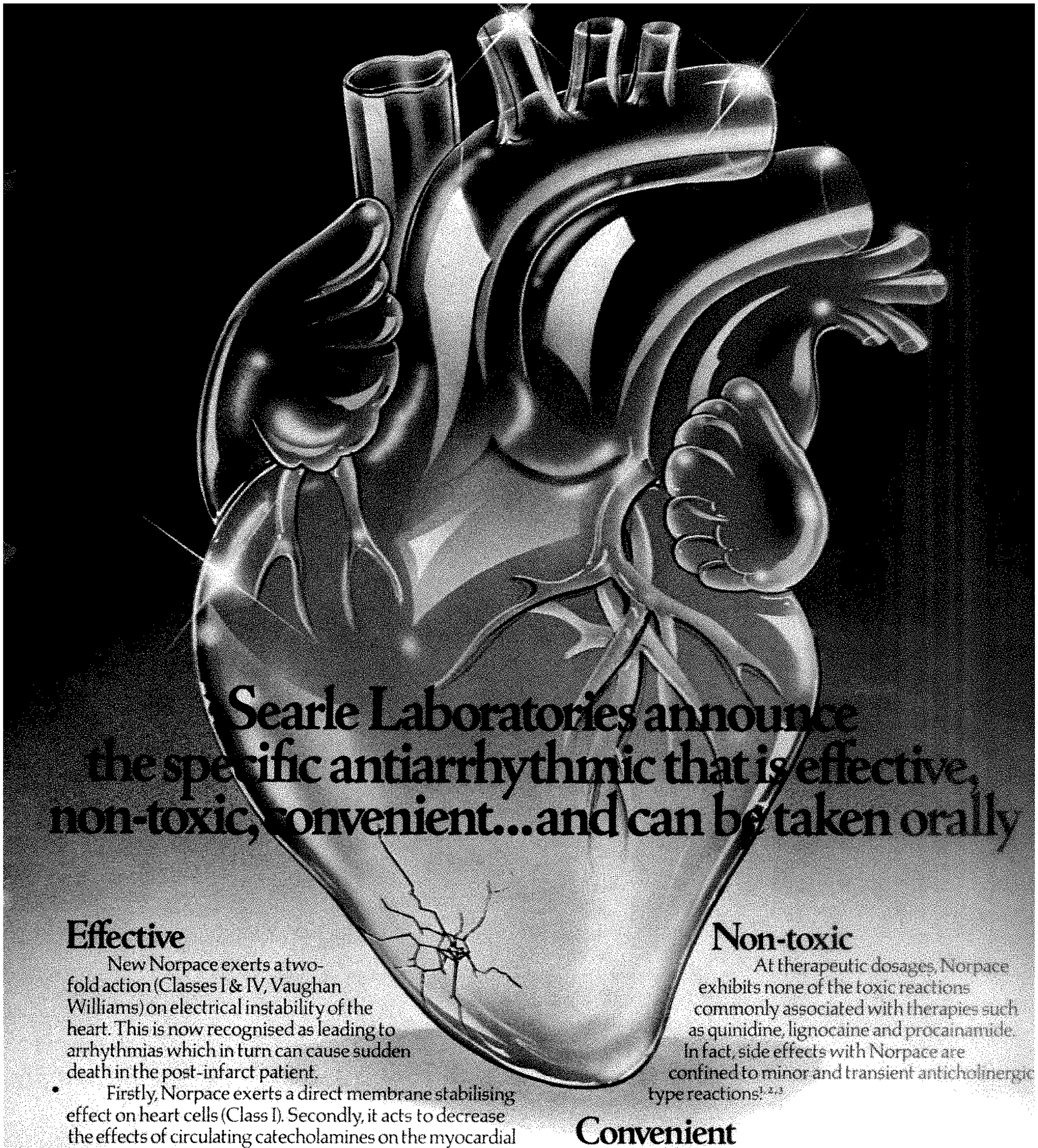

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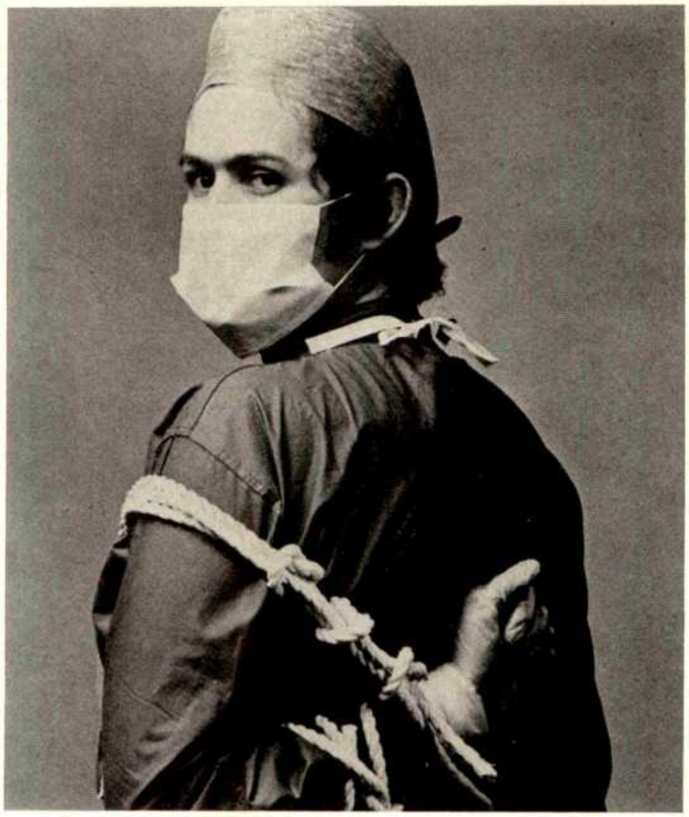

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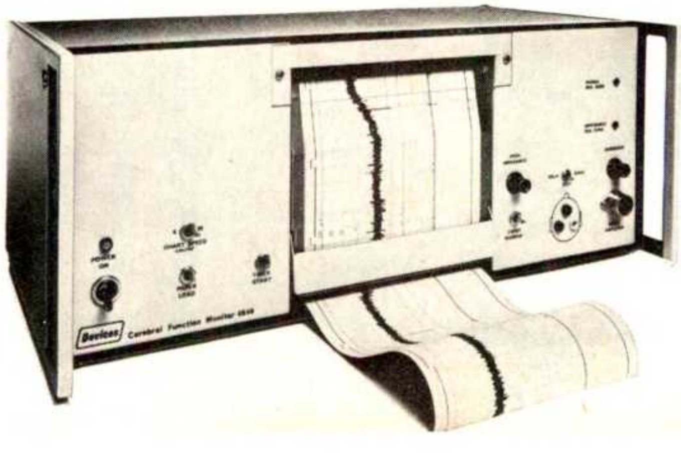

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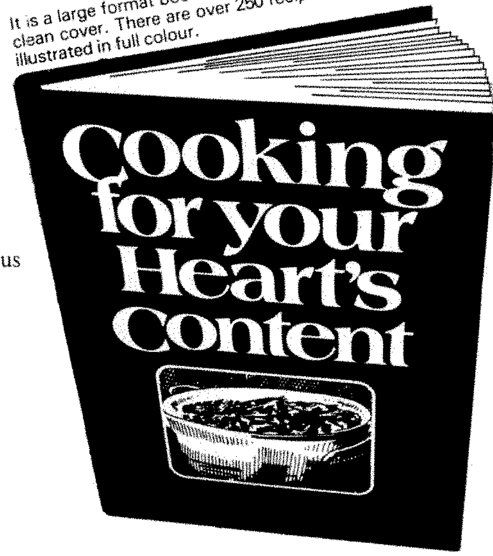

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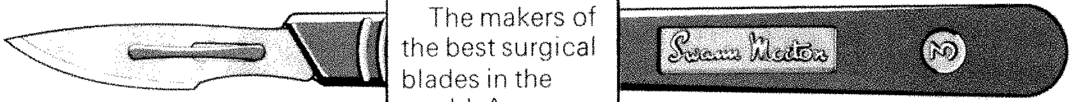

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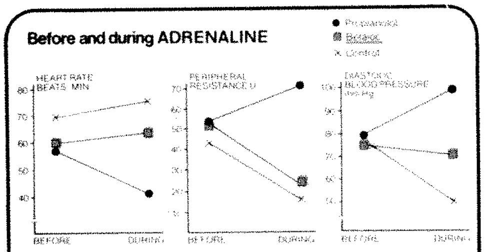

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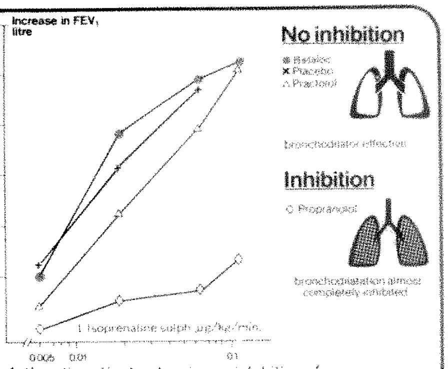

Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

[1] (1975) *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 University of Gothenburg, Sweden.

[2] Clinical Report (1975), University of Gothenburg, Sweden.

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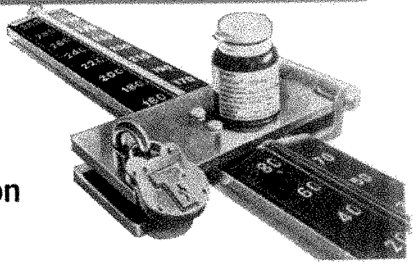

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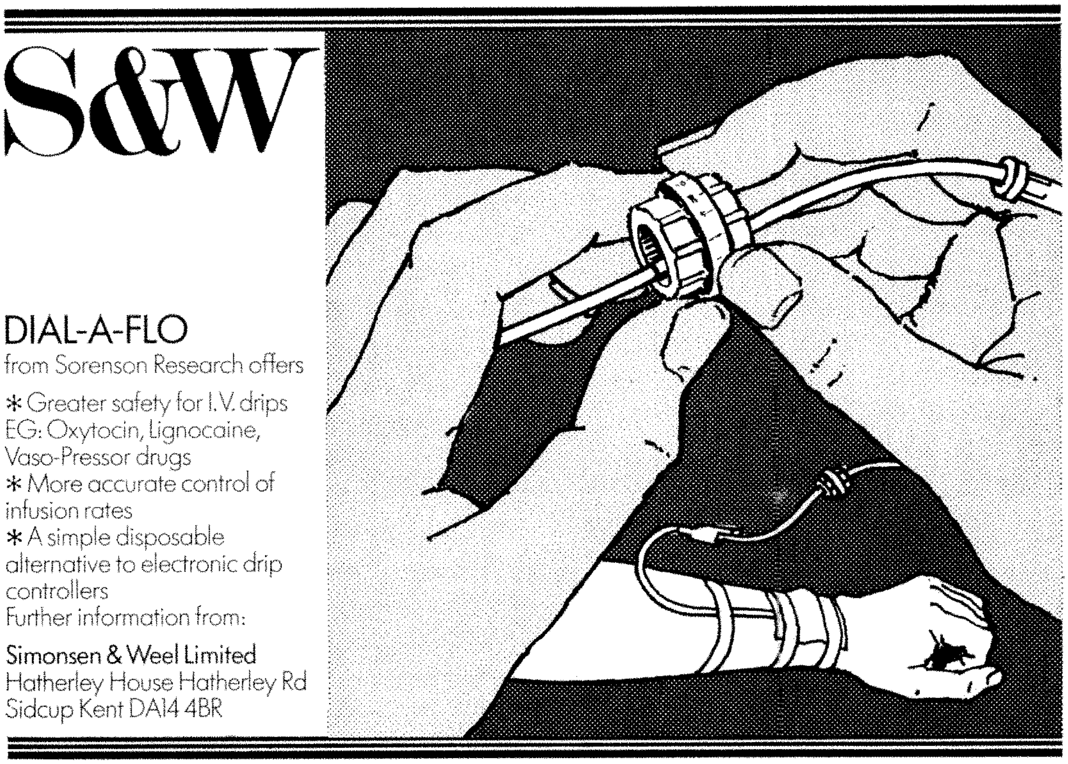

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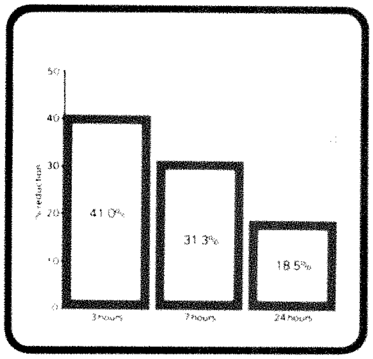

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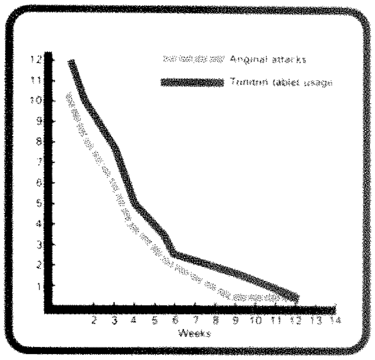
*after* Brown, H.C. et al. (1976) *Eur.J.clin. Pharmac.*, **9**, 367.



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Miller, *J. et al.* (1974) In: *Advances in Beta-adrenergic Blocking Therapy-Sotalol*, ed. Snart, A.G., 2, 43. Amsterdam: Excerpta Medica

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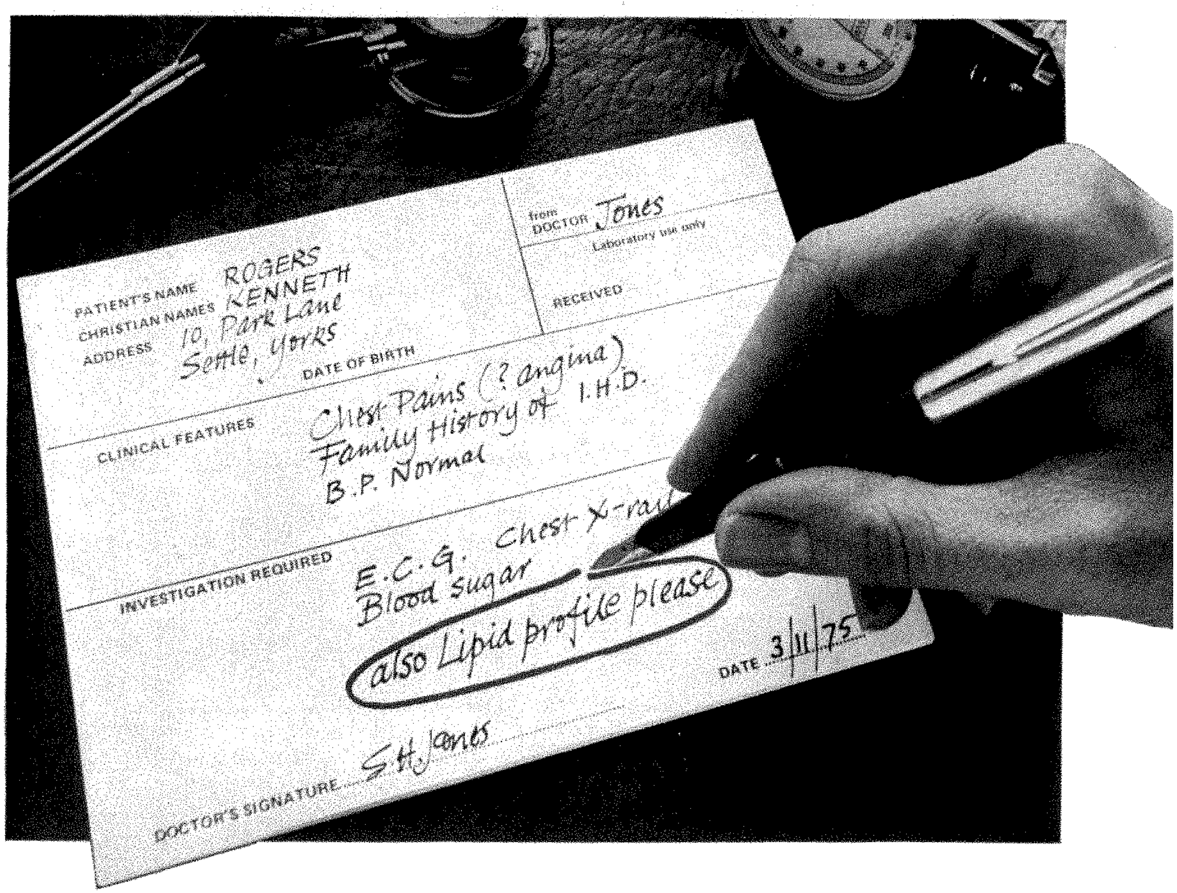

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PATIENT'S NAME ROGERS

CHRISTIAN NAMES KENNETH

ADDRESS 10, Park Lane
Settle, Yorks

DATE OF BIRTH

CLINICAL FEATURES Chest Pains (? angina)
Family History of I.H.D.
B.P. Normal

INVESTIGATION REQUIRED E.C.G. Chest X-ray
Blood sugar
also Lipid profile please

DATE 3/11/75

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REFERENCES

1. Coronary Drug Project Research Group, 1975, *Journal of the American Medical Association* 231, 360.

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*British Heart Journal*, 1976, **38**, 1109–1123.

# Anatomical study of truncus arteriosus communis with embryological and surgical considerations

Gaetano Thiene, Uberto Bortolotti, Vincenzo Gallucci, Vito Terribile, and
Piero A. Pellegrino

*From the Departments of Pathology, Cardiovascular Surgery, and Paediatrics, Medical School, University of Padua, Padua, Italy*

*Twelve specimens of truncus arteriosus communis have been studied anatomically, with special reference to the conal anatomy and to the associated cardiac anomalies which can create additional problems if surgical repair is planned. A wide spectrum of conal morphology has been observed, suggesting that differential conal absorption is a developmental characteristic of truncus arteriosus as well as of transposition complexes. The invariable absence of septation of the ventricular infundibula and semilunar valves, in spite of the variable anatomy of the free wall of the conus, indicates that all types of truncus arteriosus, ontogenetically, should be considered as a single undivided conotruncus. Various types of ventricular septal defect were found: (a) ventricular septal defect with absent crista, in which no remnants of conal septum are present; (b) supracristal ventricular septal defect, in which vestigial conal septum is seen in front of the membranous septum; (c) bulboventricular foramen, associated with univentricular origin of the truncus from the right ventricle. Frequent associated anomalies are underdevelopment of the aortic arch, truncal valve malformations, and obstructive ventricular septal defect. The AV conduction system studied in one case showed an arrangement similar to Fallot's tetralogy with the His bundle and the left bundle-branch in a safe position behind the posteroinferior rim of the defect. The postoperative fate of the frequently abnormal truncal valve and the theoretical indications for total repair for Type IV truncus are also discussed.*

The anatomical study of truncus arteriosus communis has gained great importance since total surgical correction of this malformation has become possible (McGoon, Rastelli, and Ongley, 1968; Mair *et al.*, 1974). Recent reports have emphasized that the problems facing the surgeon are related not only to the lack of partitioning between aorta and pulmonary artery, but also to the status of the truncal valve, the degree of aortic arch development, and the size of the ventricular septal defect (Becker, Becker, and Edwards, 1971; Gomes and McGoon, 1971; Mair *et al.*, 1974; Bharati *et al.*, 1974).

In addition, the morphological study of a lesion such as truncus arteriosus communis, in which partial or complete absence of division of the conotruncus is present, may help to clarify which developmental structures take part in the septation of the outflow tracts of the normal heart. With this in mind, we have also examined cases presenting with aortopulmonary septal defect or conal ventricular septal defect which are developmentally related to truncus arteriosus.

## Definition of terms

The term *conus*, embryogenetically, refers to the middle third of the bulbus cordis; it is formed by free walls (parietal conus) and by septum (conal septum) derived from the fusion of the conus ridges. Anatomically, the conus corresponds to the outflow tracts of both ventricles and conventionally it refers to the muscular cardiac segments interposed between the semilunar and atrioventricular valves; the conal septum is that portion of the ventricular septum which separates the ventricular infundibula. In the early stages of cardiac development, the atrioventricular channel is separated from the semilunar valves by the parietal conus; a process of differential absorption leads to direct fibrous continuity between mitral and aortic valves, while

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conal muscular discontinuity persists between pulmonary and tricuspid valves.

The term *truncus* indicates the distal bulbus cordis, the site of growth of the truncal ridges. Anatomically, the truncus corresponds to the semilunar valves; the truncal septum, embryogenetically derived from the fusion of the main truncal ridges, corresponds anatomically to the fibrous septum which separates the roots of the aorta and pulmonary artery. The ascending aorta and main pulmonary trunk originate from the ventral aorta (or aortic sac) and are septated, during development, by the aortopulmonary septum. The limits of truncus and aortic sac and of truncal and aortopulmonary septa are unknown. *Conotruncus* is a collective term used for the conus and the truncus, as is truncoconal septum for the conal and truncal septa.

The *crista supraventricularis* is a muscular segment of the right ventricle interposed between the tricuspid and pulmonary valves: it is a conal structure, consisting of the conal septum medially and of a parietal band derived from the right portion of the conoventricular flange, laterally. The conoventricular flange is the inner curvature of the primitive heart tube, after d-looping, and represents part of the posterior wall of the primitive undivided conus; it is thus an anatomical landmark of the parietal conus. The *septomarginal band* is a muscular trabecula of the right ventricle, formed by the septal and moderator bands, quite distinct from the crista supraventricularis, because from a developmental point of view it is not a conal structure.

## Subjects and methods

Of the 400 anatomical specimens of congenital heart diseases collected during the past 10 years in the Institute of Pathologic Anatomy of Padua University Medical School, 12 cases (3%) presented with the classical features of truncus arteriosus communis, i.e. only one arterial trunk, arising from the heart above a ventricular septal defect and giving rise to the coronary, systemic, and pulmonary circulations. Cases with pseudotruncus aorticus and pulmonalis in which the pulmonary trunk and the ascending aorta, respectively, were hypoplastic, as a result of atresia of the correspondent semilunar valve, were excluded. In addition, hearts with truncus arteriosus were compared with those with aortopulmonary septal defect or with conal ventricular septal defect, in which an isolated defect of septation of the outflow tracts of the heart was present.

The truncus arteriosus specimens were studied with reference to the patterns of origin of the pulmonary arteries; the development of the aortic arch and ductus arteriosus in relation to the type of arterio-ventricular alignment; the status of the truncal valve; the type and size of the ventricular septal defect and the morphology of the ventricular outflow tracts; the conducting tissue; the degrees of failure of septation and the pulmonary vascular bed.

## Findings

### Patterns of origin of pulmonary arteries

Using the classification of Collett and Edwards (1949), 7 cases presented with the pulmonary arteries arising from a short common pulmonary trunk (Type I). In 3 cases, the pulmonary arteries arose independently, in one case posteriorly, in another anteriorly, and in the last case on the left lateral side of the truncus arteriosus (Type II) (Fig. 1). No cases of Type III were observed, while 2 were Type IV with the pulmonary circulation supplied by arterial branches arising from the descending aorta (Fig. 2).

### Development of aortic arch and ductus arteriosus in relation to type of arterio-ventricular alignment

Four cases showed a right aortic arch, and one of these presented with an aberrant retro-oesophageal left subclavian artery. In 9 cases, the truncus arteriosus communis had a biventricular origin. In the other 3 it arose entirely from the right ventricle; in 2 of these a left aortic arch was interrupted between the left carotid and subclavian arteries (Fig. 3a), and in the third a left aortic arch was hypoplastic.

The ductus arteriosus was absent in 8 cases and hypoplastic in 1; in the remaining 3, the ductus was widely patent so that there was anatomical continuity between the heart and the descending aorta (Fig. 3a).

### Status of truncal valve

The truncal valve was bicuspid in 2 cases, tricuspid in 8, and quadricuspid in 2. The width and the length of the cusps were always unequal. In 10 cases the cusps had a fairly prominent nodular thickening along the free edge.

In a specimen with univentricular origin of the truncus from the right ventricle, the grossly nodular quadricuspid truncal valve was severely regurgitant, the right ventricular cavity was widely dilated and 'jet lesions' were present on the endocardium

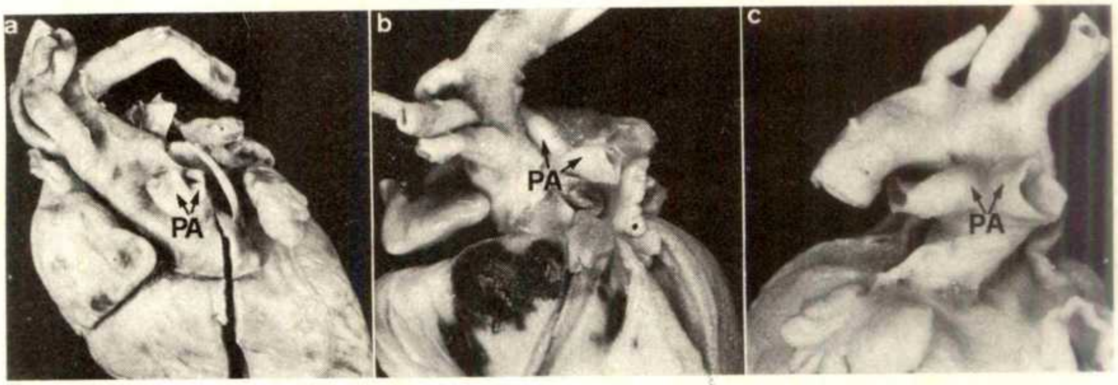


FIG. 1 *Various patterns of origin of pulmonary arteries (PA) in Type II truncus: (a) from anterior aspect of truncus, viewed from the front, (b) from left lateral aspect of truncus, viewed from the front, and (c) from posterior aspect of truncus, viewed from the back.*

(Fig. 3b). Histological examination of this valve showed conspicuous thickening by mucoid connective tissue (Fig. 4).

In a case of Type IV truncus, observed in a 29-year-old man, the tricuspid truncal valve showed moderate fusion of the cusps at the commissures and nodular calcific thickening, causing truncal valve stenosis (Fig. 5).

### Type and size of ventricular septal defect in truncus arteriosus communis and morphology of ventricular outflow tracts

Since in all 12 specimens the ventricular septal defect was located anteriorly, corresponding to the conal component of the ventricular septum, it could be regarded as a conal ventricular septal defect (Fig. 6a).

The case material was classified according to the morphology of the margins of the defect, as follows:

(a) Six cases in which the posterior margin consisted of the membranous septum, and the anterior margin consisted of the anterior conal free wall suggesting the term of 'absent crista ventricular septal defect' (Goor *et al.*, 1970) (Fig. 6b). This type is very similar to the classical ventricular septal defect observed in Fallot's tetralogy, with the difference that in this last situation the anterior margin is represented by the deviated conal septum.

(b) Three cases in which conal musculature, located in front of the membranous septum, formed the posterior rim of the defect. In this situation the ventricular septal defect may resemble a supracristal defect (Goor *et al.*, 1970) (Fig. 6c, 10a).

(c) Three cases where the roof of the defect consisted either of a conal vestige of the bulboventricular flange (1 case) (Fig. 6d) or of the anterior mitral leaflet (2 cases) (Fig. 3c) because of the right lateral displacement of the truncus. Here the ventricular septal defect constitutes the only outlet for the left ventricle, as occurs during development before the conotruncal shift towards the midline (Goor, Dische, and Lillehei, 1972; Anderson *et al.*, 1974b). This

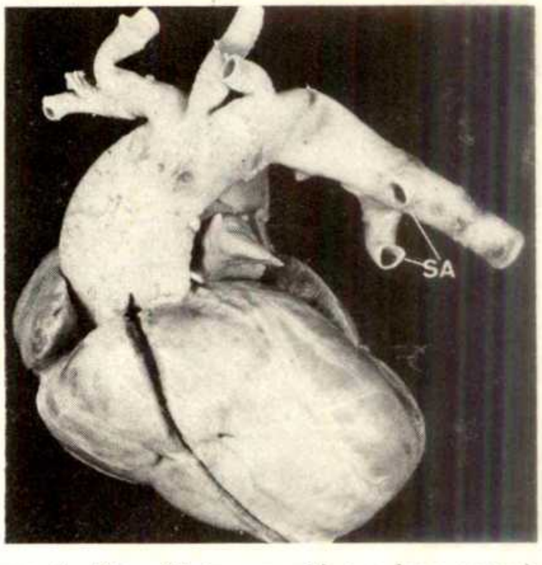


FIG. 2 *Type IV truncus with two large systemic arteries (SA) taking origin from the descending aorta and supplying the right and left lungs.*

type of defect may be regarded as a true bulboventricular foramen.

The atrioventricular component of the membranous septum was completely developed in all 12 specimens. The interventricular component was normal in the 3 cases with supracristal defect (Fig. 6a, c) and in one case of absent crista defect, where it appeared as a formed fibrous curtain in the posterior quadrant of the defect, but did not close the defect (Fig. 3b). In the other cases it was only partially developed.

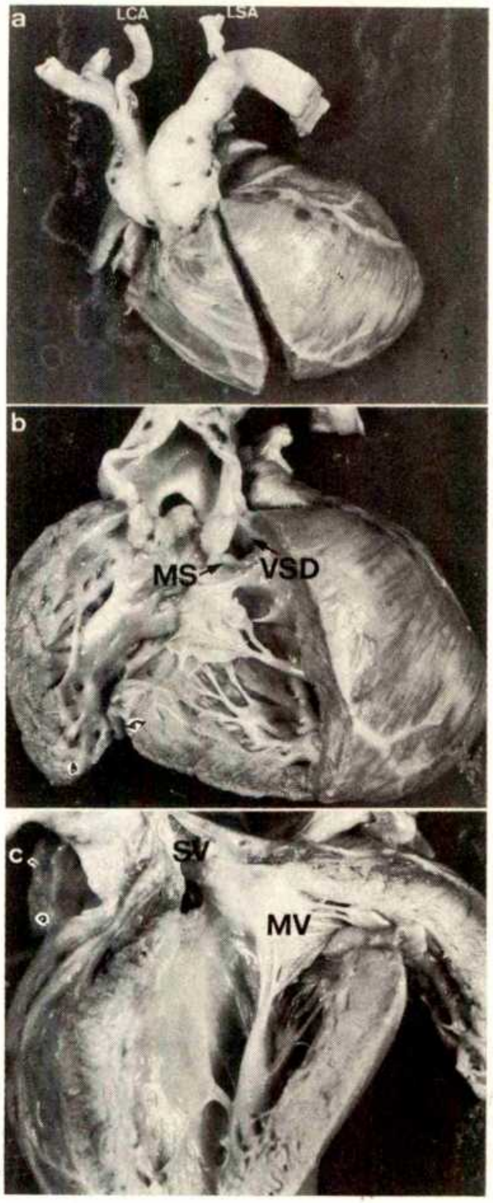


FIG. 3 *Type I truncus with interrupted left aortic arch. (a) External view showing complete interruption between left carotid (LCA) and left subclavian (LSA) arteries. (b) Right ventricle: truncus arises entirely from right ventricular cavity; quadricuspid truncal valve with thick and nodular leaflets; right ventricle is very dilated, as a result of truncal valve regurgitation, and shows endocardial 'jet lesions'; pars interventricularis of the membranous septum (MS) is normally developed, but is 'free floating' and forms the posterior rim of the ventricular septal defect (VSD). (c) Left ventricle: black probe, below semilunar valve (SV), indicates ventricular septal defect which is only outlet for left ventricle; mitral valve (MV) is in fibrous continuity with semilunar valve of truncus and forms roof of defect.*

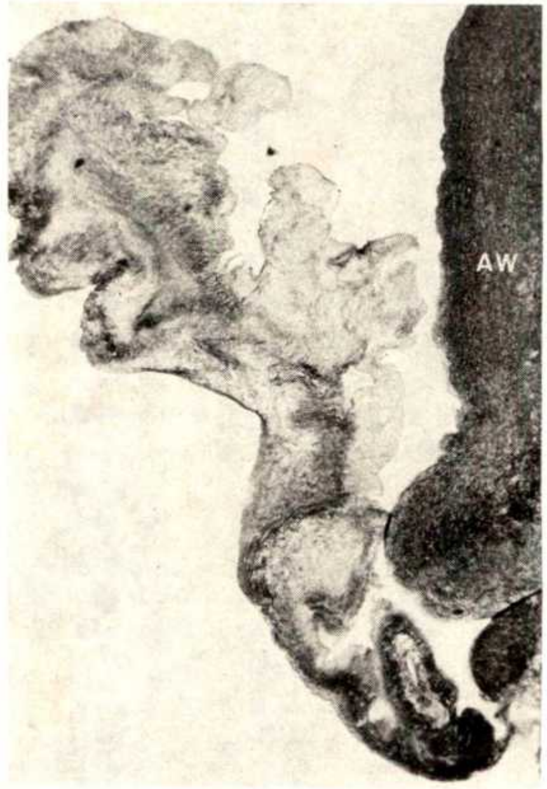


FIG. 4 *Histological appearance of truncal cusp, showing abnormal shape and severe mucoid thickening. AW=aortic wall. (Elastic-Van Gieson stain ×12.)*

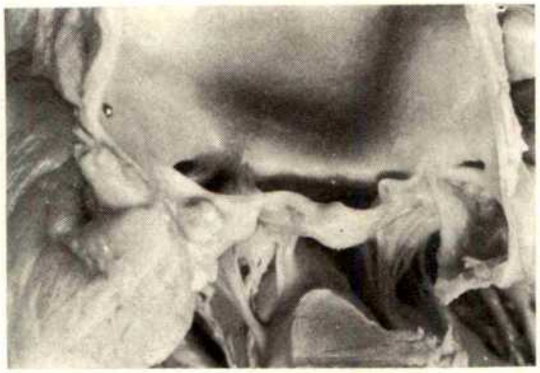


FIG. 5 *Truncal valve from 29-year-old patient with Type IV truncus: there is mild commissural fusion and nodular calcific thickening of the cusps, whose excursion is severely limited, resulting in valvular stenosis.*

Assuming that muscular structures between truncal and atrioventricular valves represent conal free walls, 6 specimens showed fibrous parietal coni, with bilateral direct continuity between the truncal and the atrioventricular valves (Fig. 7a). A more or less developed right parietal conus, with muscular discontinuity between the truncal and tricuspid valves and fibrous continuity between the truncal and mitral valves, was observed in 5 specimens. The right conal muscle often appeared as the 'crista supraventricularis', much as in the normal heart (see Fig. 10). A bilateral parietal conus was present in one case as a muscle cuff (conoventricular flange) separating the truncal valve from both atrioventricular valves (Fig. 7b).

A conal papillary muscle (Lancisi's muscle) was observed in 5 specimens. There was no correlation between its presence and the type of ventricular septal defect.

A pulmonary infundibulum, even blind or potential, was never identified as a separate entity in any of the types of truncus.

In two of the three cases with underdeveloped aortic arch and truncus arising entirely from the right ventricle, there was fibrous continuity between the mitral and truncal valves (Fig. 3c) and in the third there was one muscular parietal conus between mitral and truncal valves (Fig. 7b).

## Conducting tissue

In the case with bilateral parietal conus, the conoventricular flange was responsible for a partial obstruction of the ventricular septal defect (Fig. 6d). Serial histological examination of the conducting system showed a normally located compact AV node and the penetrating bundle passing on the left side of the central fibrous body. The branching portion of the AV bundle ran beneath the membranous septum (Fig. 8a) and passed on the left side of the crest of the still intact ventricular septum (Fig. 8b). The left bundle-branch emerged as a continuous sheet before the branching bundle reached the posteroinferior rim of the ventricular septal defect. The right bundle-branch was the direct continuation of the branching bundle (Fig. 8c): it was first observed at the posterior aspect of the ventricular septal defect, on the left of the inferior border of the defect, and penetrated the myocardium to reach the septomarginal band after a long intramyocardial course (Fig. 8d, e, f).

## Degrees of failure of septation

The conal component of the ventricular septum was partially or totally absent in all truncus arteriosus communis specimens, indicating lack of septation of the ventricular outflow tracts resulting from conal growth failure. In addition, the semilunar valves and the sinuses of the great arteries were always undivided, suggesting developmental absence also of the truncal septum.

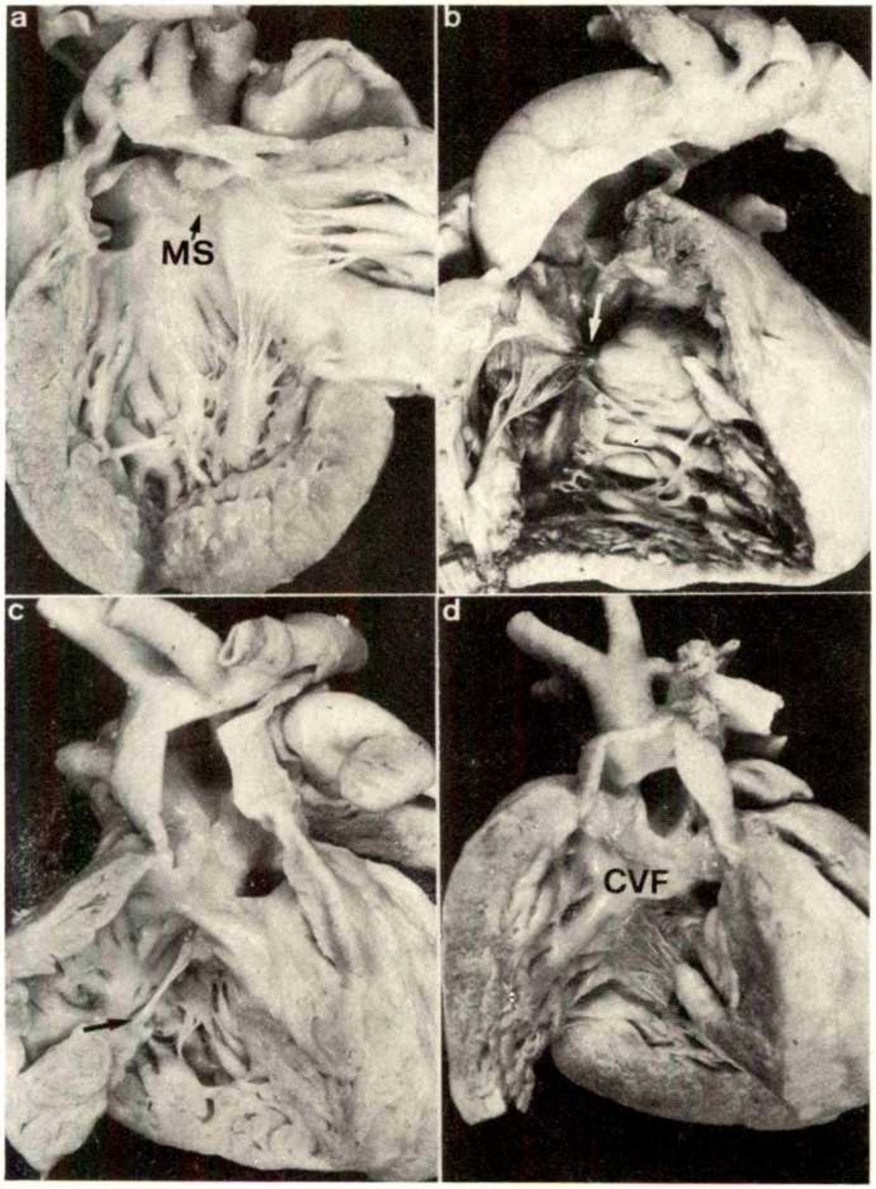
While in Type I truncus the absence of septation involved the ventricular outflow tracts, the semilunar valves, and the sinuses of the great arteries, in the other cases (Types 2 and 4) there was also no division between ascending aorta and pulmonary trunk.

Examination of those specimens showing defects which we consider developmentally related to truncus arteriosus communis disclosed normal septation of the ventricular infundibula, the semilunar valves, and the aortopulmonary sinuses in aortopulmonary window, along with a greater or lesser degree of growth failure in the wall normally separating the ascending aorta from the pulmonary trunk (i.e. aortopulmonary septum) (Fig. 9a). In addition, partial or complete failure of division of the ventricular outflow tracts was observed in the conal ventricular septal defects, though the semilunar valves and the great arteries were normally divided (Fig. 9b).

## Pulmonary vascular bed

Patients with type 1 and 2 truncus at death ranged in age from 2 days to 3 months. In each case histological examination of the lungs revealed grade 1 changes of the small arteries and arterioles (Heath and Edwards, 1958).

The age at death of the two patients with Type IV truncus was 1 and 29 years; the former died with signs of congestive heart failure, and the latter as a result of cerebral abscess and severe hypoxia. The lungs were available for gross and histological examination in the first case only. Gross examination of the heart showed conspicuous dilatation of the left ventricle, suggesting the presence in life of a large left-to-right shunt even though no true pulmonary arteries took origin from the common trunk. The pulmonary circulation was sustained by two large systemic arteries arising from the descending aorta, one for each lung (Fig. 2). The left lung circulation was visualized by post-mortem injection of radio-opaque material into the large systemic artery, and a normal lobar distribution without tortuosity was observed. Histological examination showed no abnormalities in the arterial wall but there was medial hypertrophy of pulmonary arterioles.



## Discussion

### Conal anatomy in truncus arteriosus communis and its morphogenetic significance

The morphology of the ventricular outflow tract in truncus arteriosus communis is variable. The posterior wall is usually fibrous with direct continuity between the truncal and the mitral and tricuspid valves, indicating that the embryonic conoventricular flange has undergone complete absorption (Goor *et al.*, 1972; Anderson *et al.*, 1974b). Rarely, this structure is seen as a muscular mass interposed bilaterally between the truncal valve and the AV valves. In the other specimens, while there is fibrous continuity between truncal and mitral valves, a muscular structure separates the truncal from the tricuspid valve, often resembling the crista supraventricularis of the normal heart. Different degrees of infundibular muscular development may also be seen in the anterior wall of the common outflow tract. These findings suggest that a wide spectrum of conal anatomies exists in truncus arteriosus communis and that a differential conal absorption is a developmental characteristic of this malformation as well as of the transposition complexes (Goor and Edwards, 1973; Anderson *et al.*, 1974a; Thiene, Razzolini, and Dalla-Volta, 1976).

Various patterns of truncoventricular alignment may be observed in truncus arteriosus communis. The fact that univentricular origin of the truncus from the right ventricle may be associated with either the persistence of the left portion of the conoventricular flange or its complete disappearance, suggests that the process of differential conal absorption, which normally occurs during the developmental shaping of the infundibula (Goor *et al.*, 1972; Anderson *et al.*, 1974b), is not the only factor playing a role in the transfer of the posterior conus above the left ventricle, and may not be involved at all. Therefore, as we recently suggested in a study on transposition complexes (Thiene *et al.*, 1976), differential conal absorption may not influence the arterioventricular alignment.

### Truncus arteriosus communis: extreme hypoplasia or absent septation of conus?

In spite of the variability of conal anatomy, the basic defects in truncus arteriosus communis are always in a high anterior ventricular septal defect and a common semilunar valve, indicating lack of septation of the embryonic conotruncus. For this reason, truncus arteriosus communis may be defined, morphogenetically, as a single undivided conotruncus (M. V. de la Cruz, 1975, personal communication).

The view propounded by Van Praagh and Van Praagh (1965) that truncus is a pseudotruncus aorticus (pulmonary atresia + ventricular septal defect), developmentally determined by an extreme hypoplasia of the subpulmonary conus, is not supported by our finding in one case of a well-formed bilateral muscular conus.

The fact that there are three or four truncal valve cusps more commonly than two has been used in support of the view that the truncal valve might be an aortic valve (Van Praagh and Van Praagh, 1965). We believe that if the main truncal ridges do not develop at all a bicuspid truncal valve results; if one or both main truncal ridges grow without fusing, the resulting cusps are three or four.

### What is crista supraventricularis in truncus arteriosus communis?

The muscular structure intervening in five of our cases of truncus arteriosus communis between

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← FIG. 6 *Various types of ventricular septal defect in truncus. (a) Left ventricular view of specimen, showing high anterior location of defect corresponding to conal component of ventricular septum, and in front of membranous septum (MS). (b) Absent crista ventricular septal defect: posterior rim of defect is represented by confluence (white arrow) of the anterior and septal leaflets of the tricuspid valve with membranous septum and medial cusp of mitral valve. (c) Supracristal ventricular septal defect: a muscular structure located in front of the membranous septum forms posterior edge of ventricular septal defect; black arrow indicates hypoplastic anterior right papillary muscle. (d) Bulboventricular foramen: truncus arises entirely from right ventricle and ventricular septal defect is only outlet for left ventricle; because of persistence of conoventricular flange (CVF), roof of defect is formed by conal muscle; resulting ventricular septal defect is partially obstructive and truncal valve is bicuspid. Because of these anatomical features, this specimen is true fetal common conotruncus (absent truncal and conal septation, persistence of conoventricular flange, and univentricular origin of truncus from bulbus cordis).*

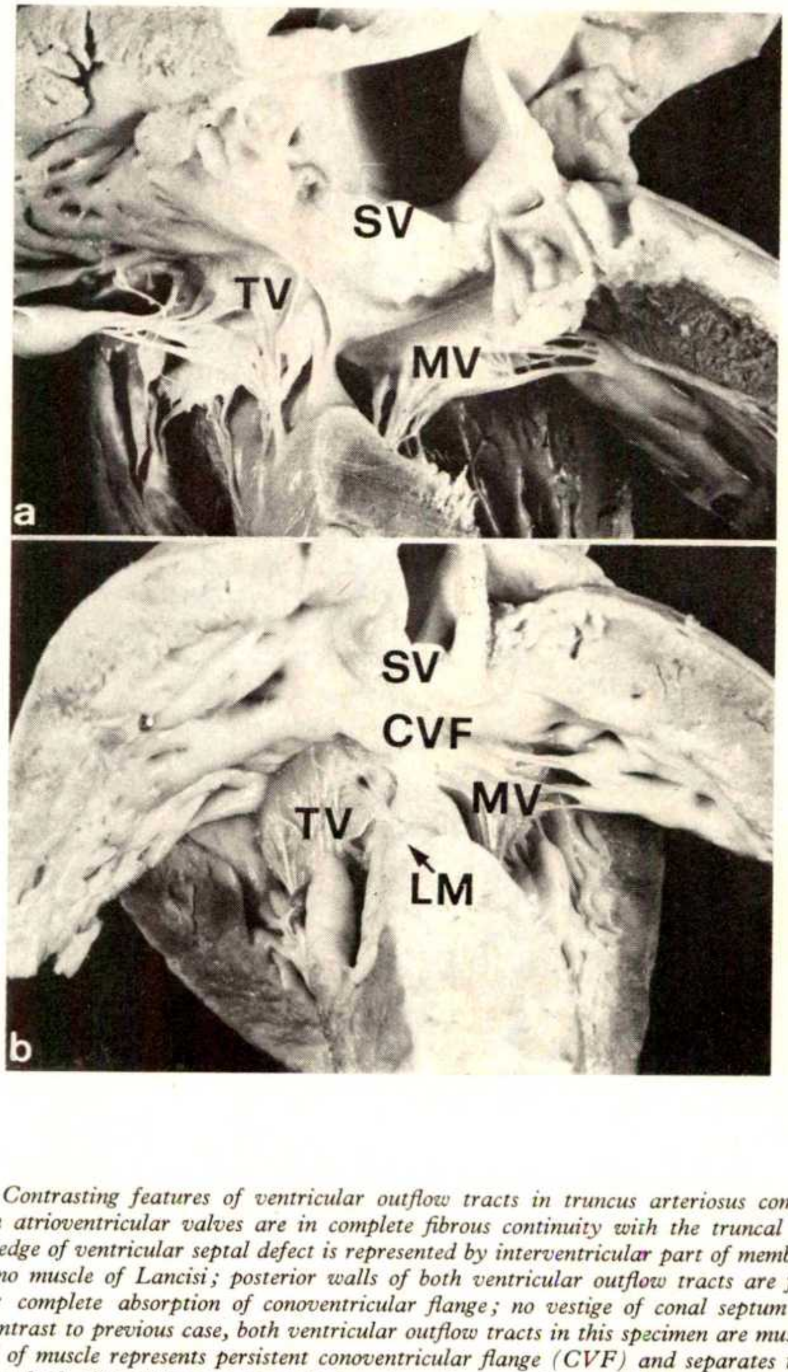

FIG. 7 *Contrasting features of ventricular outflow tracts in truncus arteriosus communis. (a) Both atrioventricular valves are in complete fibrous continuity with the truncal valve; posterior edge of ventricular septal defect is represented by interventricular part of membranous septum; no muscle of Lancisi; posterior walls of both ventricular outflow tracts are fibrous, indicating complete absorption of conoventricular flange; no vestige of conal septum exists. (b) In contrast to previous case, both ventricular outflow tracts in this specimen are muscular; large cuff of muscle represents persistent conoventricular flange (CVF) and separates truncal valve from both AV valves; posteroinferior edge of ventricular septal defect is formed by confluence of mitral and tricuspid septal leaflets with membranous septum; truncal valve is bicuspid and truncus arises entirely from right ventricle (same specimen as Fig. 6d); 'conal' papillary muscle is seen, though conal septum is totally absent. LM = Lancisi's muscle, MV = mitral valve, SV = semilunar valve of truncus, TV = tricuspid valve.*

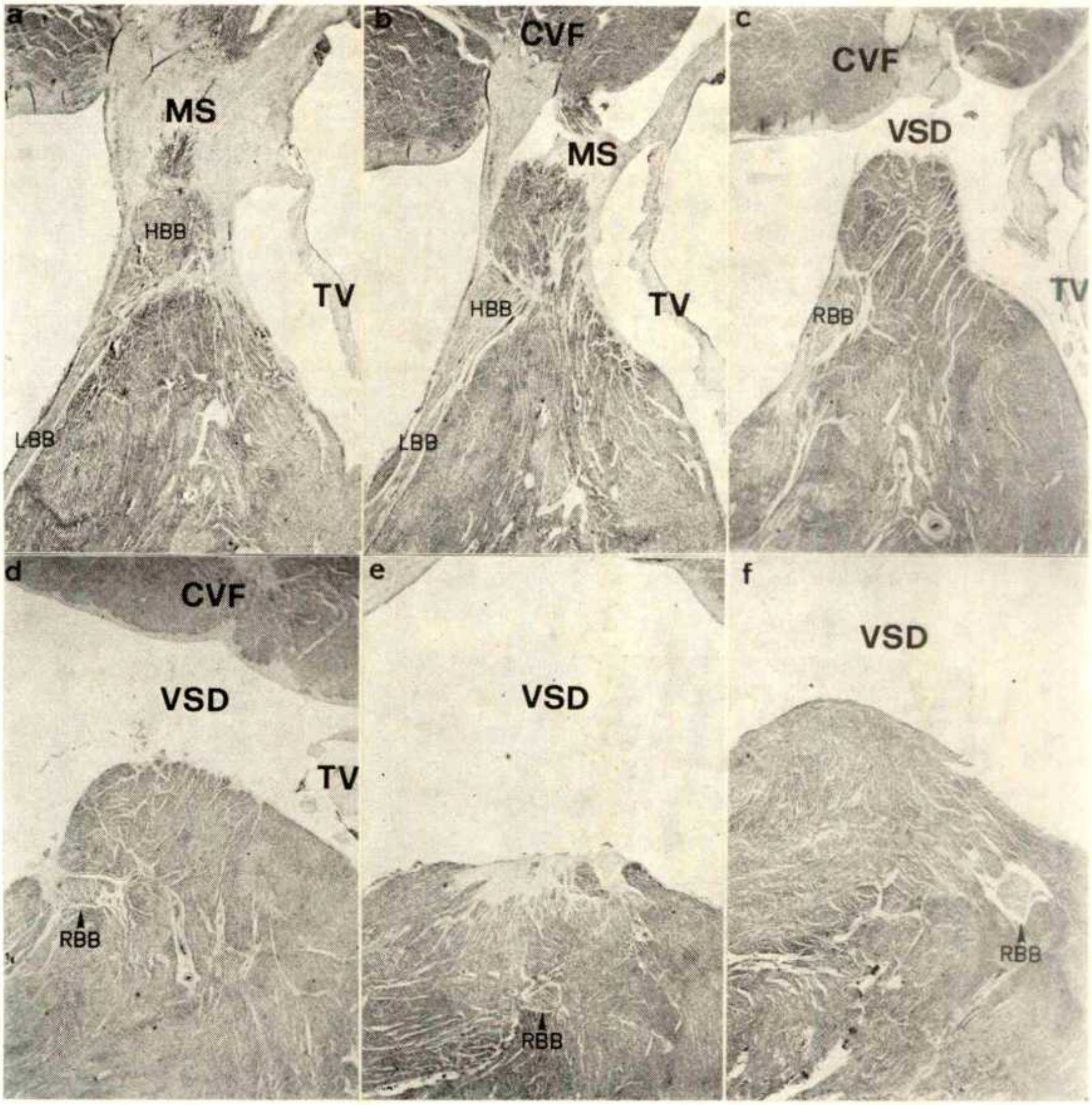

FIG. 8 *Microphotographs of AV conducting system, from case with partially obstructive ventricular septal defect, studied with serial histological sections. Junctional area sectioned in frontal plane from posterior to anterior. (a) and (b) Branching main bundle runs beneath and on left of membranous septum, giving rise to left bundle-branch, then passing to left of crest of posterior muscular septum. In serial sections sheet-like left branch originates before ventricular septal defect appears. (c) First appearance of the ventricular septal defect, posteriorly: left bundle-branch can no longer be seen; right bundle-branch evident on left side of crest of ventricular septum as direct continuation of branching main bundle. (d, e, f) Serial sections in posteroanterior sequence, showing intramyocardial course of cord-like right bundle-branch, which moves from left to right; only right bundle-branch is related to inferior border of ventricular septal defect. CVF = conoventricular flange, HBB = branching His bundle, LBB = left bundle-branch, MS = membranous septum, RBB = right bundle-branch, TV = tricuspid valve, VSD = ventricular septal defect.*

truncal and tricuspid valves appeared in some of these to be a well-formed muscular mass resembling the 'crista supraventricularis'. This was situated in front of the membranous septum and extended laterally into the right ventricular free wall in a similar fashion to the parietal band of the normal heart (Fig. 10). Goor (1972) considers this structure in truncus arteriosus communis to be entirely derived from the conal septum, probably the dextrodorsal conus ridge. On the other hand, Van Praagh and Van Praagh (1965) regard this as the posterior division of the septal band and hence of non-conal origin. R. H. Anderson (1975, personal communication) believes that the truncal valve is separated from the tricuspid valve by the right margin of the conoventricular flange, while a posterior extension of the septal band separates the membranous septum and the tricuspid valve from the rim of the defect. We hold that, like the crista supraventricularis of the normal heart (Anderson *et al.* 1974b; Becker, Connor, and Anderson, 1975), it is a conal structure in which the part anterior to the membranous septum is a vestige of the conal septum, while the lateral extension represents the persistence of the right side of the conoventricular flange. If this is true, then the ventricular septal defect in tetralogy of Fallot should be considered an intracristal defect in those cases in which conal muscle is situated in front of the membranous septum (Rosenquist *et al.*, 1973).

## Lancisi's muscle: conal or non-conal papillary muscle?

The muscle of Lancisi (or right medial papillary muscle) is thought to be derived from the conal septum; according to Van Mierop (1970), this muscle is always absent in the tetralogy of Fallot, where the conal septum is anteriorly deviated, thus confirming its conal origin. On the contrary, we have identified a Lancisi's muscle in truncus arteriosus communis specimens where no trace of conal septum was present, i.e. those cases where no muscle was seen in front of the membranous

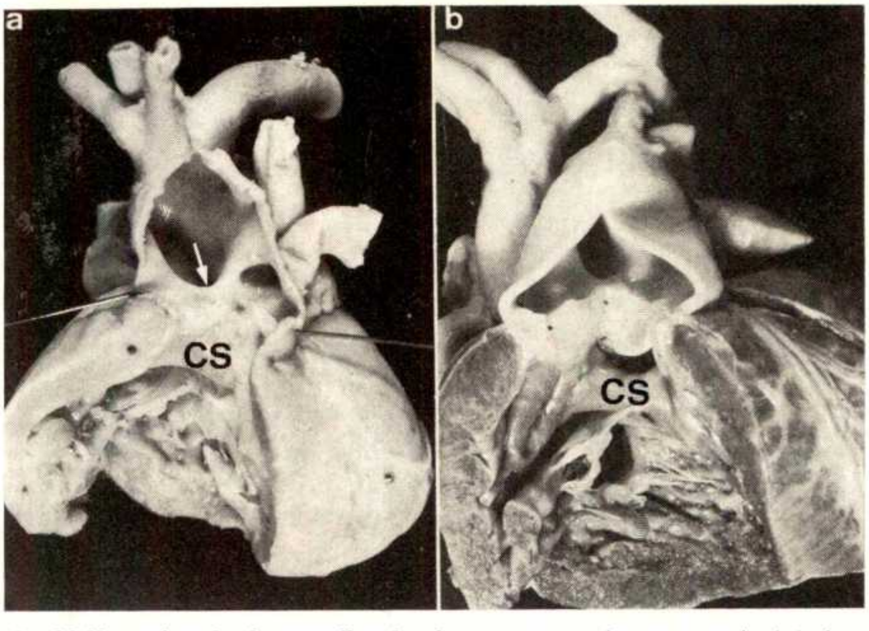

FIG. 9 *Malformations developmentally related to truncus arteriosus communis. (a) Aortopulmonary septal defect: though both infundibula and the semilunar valves are normally divided, a large communication exists between ascending aorta and common pulmonary trunk. Note that the sinus portions of aorta and pulmonary artery are separated by a fibrous septum (white arrow); this probably represents the most cranial extension of the truncal septum and indicates the limit between truncal and the aortopulmonary septa. (b) Isolated supracristal ventricular septal defect: large communication between infundibula of right and left ventricles; semilunar valves, ascending aorta, and pulmonary trunk normally separated. CS = conal septum.*

septum (Fig. 7b). In our opinion, these findings suggest that Lancisi's muscle from a developmental viewpoint is not a 'conal' papillary muscle.

## Spectrum of defects of septation in truncus arteriosus communis and related malformations

From the examination of specimens of hearts with truncus arteriosus communis and related malformations, the existence of three different developmental components, taking part in the division of the outflow tracts of the heart, may be postulated (Van Mierop and Gessner, 1972): the conal septum, separating the infundibula; the truncal septum, separating the semilunar valves and the sinus portions of aorta and pulmonary artery; and the aortopulmonary septum separating the ascending aorta from the pulmonary trunk. Though the embryological border between truncus and aortic sac has not yet been defined, our findings suggest that the sinus portion of the great arteries is derived from the embryological truncus, while the tubular portion is derived from the aortic sac.

In truncus arteriosus communis there is a lack of septation of the truncus and conus, resulting from a failure of development of the truncal and conal septa, while the aortopulmonary septum may (Type I) or may not (Types II, III, IV) have developed. On the other hand, in the cases of aortopulmonary window and conal ventricular septal defect, there is an isolated failure of growth of greater or lesser degree of the aortopulmonary and conal septa, respectively. Thus, in aortopulmonary septal defect truncal and conal septa are usually well formed, with resulting normal separation of the ventricular infundibula and semilunar valves; in a similar manner, in conal ventricular septal defects the aortopulmonary and truncal septa have developed normally.

Fig. 11 shows all the possible malformations which may theoretically occur as a result of single or multiple failures of the three developmental septation components. A malformation featuring

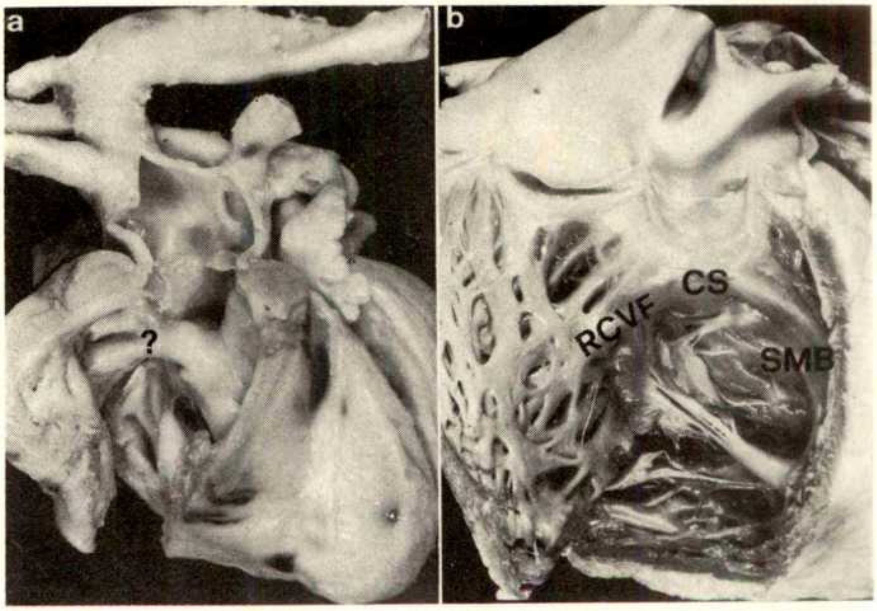

FIG. 10 *(a) Truncus arteriosus—right ventricular outflow tract: question mark indicates thick muscular structure, partly situated in front of membranous septum and extending laterally towards ventricular free wall; Lancisi's muscle is present below that structure. Ventricular septal defect resembles a supracristal ventricular septal defect. (b) c.f. right ventricular outflow tract in normal heart. This muscular mass in truncus is similar to crista supraventricularis of normal heart. Portion of normal crista in front of membranous septum may be vestige of proximal conal septum (CS) in its dextrodorsal conus ridge, while lateral extension or parietal band may be remnant of right portion of conoventricular flange (RCVF); septal extension is septomarginal band (SMB).*

separated ventricular infundibula (normally formed conal septum) and a common semilunar valve (absent truncal septum), with or without aortopulmonary septum, has never been reported. In addition, aortopulmonary window might exist together with conal ventricular septal defect; in fact, only membranous ventricular septal defects have been described associated with aortopulmonary window (Tandon *et al.*, 1974). We suggest that these 'missing links' in congenital heart diseases may exist, though examples have not yet been reported.

## What is Type IV truncus arteriosus communis?

There is no agreement on whether or not Type IV lesions should be included in truncus arteriosus communis. Macartney, Deverall, and Scott (1973) took the view that Type IV truncus should not be regarded as a form of truncus arteriosus communis; the fourth and sixth aortic arches are not 'communis' since there is agenesis of the latter. Type IV has been called 'solitary aorta associated with absence of the pulmonary arterial system' (Van Praagh and Van Praagh, 1965), 'extreme

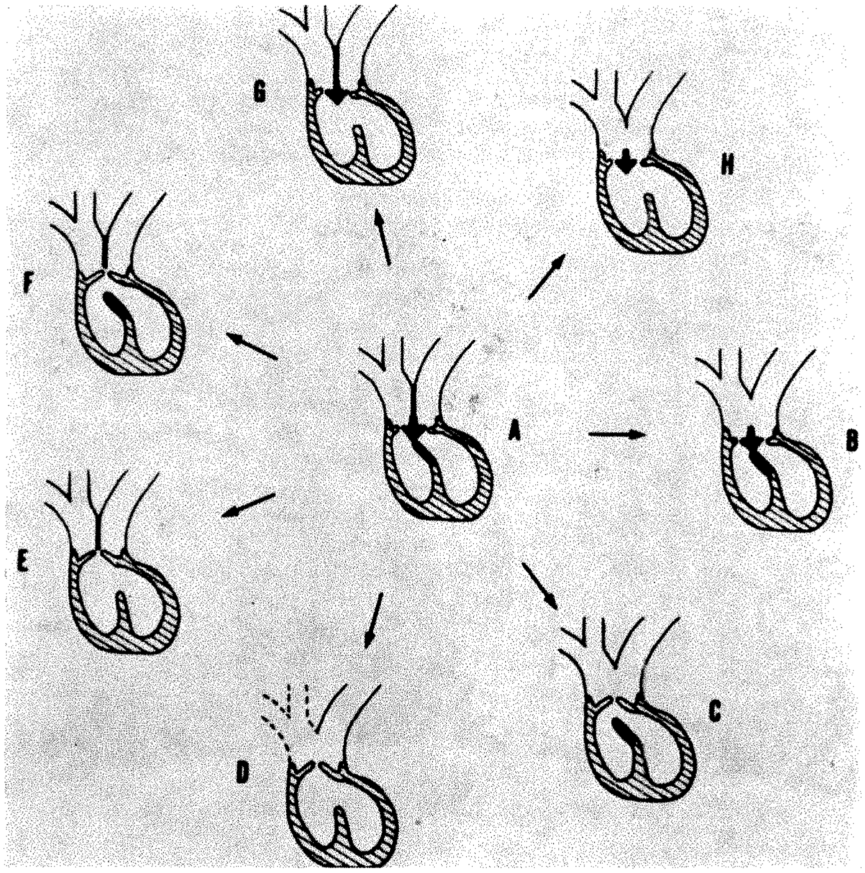

FIG. 11 *Schematic representation of all theoretical malformations derived from single or multiple developmental failure of conal, truncal, and aortopulmonary septa. (A) normal heart; (B) the isolated aortopulmonary septal defect; (C) absent truncal and aortopulmonary septa, with normally developed conal septum (not described so far); (D) Type II, III, IV truncus; (E) Type I truncus; (F) isolated truncal septal failure (not described); (G) isolated conal septal defect; (H) associated aortopulmonary and conal septal defects (not reported). (To simplify the drawings, the various septa are represented as totally present or absent.)*

pulmonary atresia similar to pseudotruncus associated with agenesis of pulmonary artery' (Stuckey, Bowdler, and Reye, 1968; Macartney *et al.*, 1973), and 'true truncus arteriosus communis associated with bilateral agenesis of the sixth aortic arch' (Collett and Edwards, 1949; Bharati *et al.*, 1974). Because of the lack of pulmonary trunk remnants and the absence of a pulmonary infundibulum, we do not consider our cases as examples of extreme tetralogy of Fallot. No signs of truncoconal septation were present, indicating a complete failure of partitioning of the conus and truncus, as in the other types of truncus arteriosus communis. Accepting the hypothesis that Type IV is a true truncus arteriosus communis, we consider that the absence of the sixth aortic arches must be regarded as an additional developmental deficiency in these cases. Thus, in Type IV truncus there is a single, undivided conotruncus, associated with an agenesis of the sixth aortic arches.

There are conflicting views regarding the nature of the arteries supplying the lungs in Type IV truncus. In the case where the left pulmonary circulation was demonstrated *post mortem*, the systemic arteries to the lungs arose from the descending aorta, entered the hila, and anastomosed directly with the arteries normally branching in the parenchyma. For this reason, we cannot regard these as true bronchial arteries, a view shared by Macartney *et al.* (1973). We believe that this systemic blood supply to the lungs in Type IV truncus is derived from a direct embryological vascular connexion between the dorsal aorta and the pulmonary plexus, as an alternative to the undeveloped sixth aortic arches. According to Jefferson, Rees and Somerville (1972), these vessels may be derived from persistent intersegmental branches of the dorsal aorta which represent the primitive blood supply to the lungs in early stages of development (Boyden, 1970). If the ventral portion of the sixth aortic arch is absent and the dorsal portion develops, the systemic circulation to the lungs in Type IV truncus may be supplied by bilateral persistent ductus arteriosus, as described by Murray and co-authors (1970).

## Underdevelopment of aortic arch in truncus arteriosus communis

Hypoplasia or interruption of the aortic arch was observed in 3 of our cases, and in 14·4 per cent of cases in the extensive necropsy series recently reported by Bharati *et al.* (1974). In our specimens, the underdevelopment of the aortic arch was also associated with a widely patent ductus arteriosus, confirming the rule that there is an inverse relation between the development of the fourth and sixth aortic arches in truncus arteriosus communis (Van Praagh and Van Praagh, 1965). As suggested by Van Mierop (1970), the fetal persistence of both these arches in truncus arteriosus communis is superfluous, because the ventricular outflow tracts and the ventral aorta are not divided and two connexions with the descending aorta are not necessary. We have emphasized (Thiene, Cucchini, and Pellegrino, 1975) that underdevelopment of the aortic arch in truncus arteriosus communis seems to be constantly associated with a univentricular origin of the truncus from the right ventricle, suggesting that the right lateral displacement of the truncus results in an uneven distribution of the common blood flow between the ascending aorta and the pulmonary artery; consequently, the predominant flow is from right to left through the ductus arteriosus, predisposing to the involution of the fourth aortic arch. Origin of the truncus arteriosus communis from the right ventricle was present in all our three cases, and also in those reported cases in which the alignment of the truncus with the ventricles was described in detail (Newcombe *et al.*, 1961; Steiner and Finegold, 1965). This association warrants further study and confirmation.

## Surgical considerations

The transformation of the truncus and truncal valve, respectively, into aorta and aortic valve and the incorporation of the ventricular septal defect into the left ventricular outflow tract, represent the main steps in the total correction of truncus arteriosus communis (McGoon *et al.*, 1968). Consequently, associated anomalies of the aorta, of the truncal valve, and of the ventricular septal defect may create additional problems for the surgeon.

Origin of the truncus entirely from the right ventricle implies that the ventricular septal defect, as a bulboventricular foramen, functions as the only outlet for the left ventricle. If the size of the defect is inadequate, thus obstructing the left ventricular outflow, surgical enlargement must be considered while planning the radical operation; under these circumstances, knowledge of the location of the conducting tissue is important for the surgeon. In the specimen studied by serial histological sections, the His bundle ran posterior to the ventricular septal defect and the left bundle-branch originated from the branching bundle before reaching the ventricular septal defect. Apart from the aberrant course of the right bundle-branch, these findings are similar to those described in hearts with Fallot's tetralogy or isolated membranous ventricular septal defects (Truex and Bishof, 1958; Lev, 1959; Visioli, Baragan, and Lenègre, 1962; Titus, Daugherty, and Edwards, 1963; Latham and Anderson, 1972), in which the perforating and the branching positions of the AV bundle were related to the posteroinferior margin of the septal defect. From a surgical point of view this implies that the main bundle and the left bundle-branch are in a 'safe' position, while only the right bundle-branch seems to occupy the area at risk in the inferior border of the ventricular septal defect. Latham and Anderson (1972) have documented pathologically a case in which intraoperative trauma to the right bundle-branch produced a haematoma which tracked back to the branching AV bundle and caused heart block. Thus, if enlargement of the ventricular septal defect is needed in truncus arteriosus communis, the manoeuvre should involve only its anterosuperior quadrant or the conoventricular flange if present, with avoidance of trauma to the inferior border of the defect.

Interruption or tubular hypoplasia of the aortic arch represents a severe additional lesion. So far, only 3 cases of total repair of truncus arteriosus communis associated with interrupted aortic arch have been reported (Mair *et al.*, 1974). The additional association of origin of the truncus from the right ventricle in these cases complicates the problem further, especially if the ventricular septal defect needs to be enlarged.

The truncal valve was abnormal in most of our specimens, and abnormal function of the truncal valve has also been frequently described in clinicopathological reports (Tandon, Hauck, and Nadas, 1963; Deely, Hagstrom, and Engle, 1963; Victorica *et al.*, 1969; Burnell, McEnery, and Miller, 1971; Gelband, Van Meter, and Gersony, 1972). In addition to those cases of gross dysfunction, which may require valve replacement at the time of total correction, increasing the surgical risk, the long-term effects of minor abnormalities should be carefully evaluated. One of our patients, a 29-year-old man, presented with a moderate truncal valve stenosis and nodular calcification of the cusps. As suggested by Becker *et al.* (1971), nodular thickening of the truncal valve may be an acquired lesion resulting from haemodynamic stress in the presence of a pre-existing developmental malformation. The state of the truncal valve should be taken into account when assessing the prognosis after operation in these cases.

Reconstruction of continuity between the right ventricle and the aortopulmonary collateral vessels might theoretically be indicated in Type IV cases, because of the direct anastomoses between the thoracic aorta and the pulmonary arterial bed. However, the site of origin, the multiplicity of the vessels, and the frequent stenoses at the lung hila precluded surgery in almost every case (Macartney *et al.*, 1973; Chesler, Matisonn, and Beck, 1974); to our knowledge, only one such patient has been successfully operated (McGoon, Wallace, and Danielson, 1973). However, the patient whose heart is shown in Fig. 2, who had a large left-to-right shunt causing lethal left ventricular failure, could have been an ideal candidate for correction. We agree with Chesler *et al.* (1974) that direct selective catheterization and arteriography of these systemic collateral vessels is essential in the investigation of these patients for operation.

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# Double outlet right ventricle
## *Study of 27 cases*

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*Out of 1610 children's hearts with congenital malformations there were 27 specimens showing double outlet right ventricle. Cases with dextrocardia, situs inversus, or l-ventricular loop were excluded. Anatomical examination was performed with particular reference to the infundibular region, the great vessels, and the ventricular septum. The commonest associated malformations were ventricular septal defect and pulmonary stenosis. Aortic stenosis was the predominant finding in those cases dying in the neonatal period. An aortic conus was associated with pulmonary stenosis, ventricular septal defect, and d-transposition, a pulmonary conus with ventricular septal defect and a double conus with stenosis of either great vessel. The anterior vessel always had a muscular conus and the posterior vessel was commonly stenotic.*

The term 'double outlet right ventricle' (DORV) signifies that both great arteries arise completely from the morphological right ventricle and that the only outlet, if any, for the morphological left ventricle is a ventricular septal defect (Witham, 1957). Other anomalies may be associated and should be specified (Neufeld, Dushane, and Edwards, 1961a). DORV is distinguished from the tetralogy of Fallot with extreme dextroposition of the aorta, as there is loss of fibro-membranous continuity between the aortic and mitral valves and the aorta arises completely from the right ventricle with no override of the ventricular septal defect. Similarly, transposition of the great arteries with ventricular septal defect and extreme dextroposition of the pulmonary artery differs from DORV in which the pulmonary artery does not override the ventricular septal defect. Again, the absence of override is of particular importance in distinction of DORV from the Eisenmenger complex and the Taussig-Bing malformation (Van Praagh, 1968).

Other definitions for DORV have been used, reflecting the wide spectrum of bulboventricular malformations, and some are atypical cases or have features of other types of anomaly (Anderson *et al.*, 1974).

We describe in this paper some anatomical features in 27 cases of DORV, as defined above, which have particular relevance to the clinical diagnosis and surgical treatment of the condition.

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### Material and methods

The 27 specimens of DORV were encountered among an anatomical review of 1610 hearts with congenital malformations: 910 from the Children's Hospital, Birmingham, and 700 from the Hospital Infantil, Madrid. Eleven of the patients died in the first 4 weeks of life and only 4 survived more than 1 year (Table 1).

All cases conforming to the definition given above (both great arteries arose entirely from the morphological right ventricle and showed no overriding) and having situs viscero-atrial solitus, laevocardia, and d-ventricular loop (Van Praagh *et al.*, 1964a) were included.

Particular attention was paid to the morphology of the right ventricle and outflow tracts, as described by Lev (1954) and by Van Praagh *et al.* (1964b). The relation of the great arteries to each other and to the conal anatomy were carefully noted, as was the relation of the semilunar valves to the atrioventricular valves. All associated anomalies were carefully examined.

Hypertrophy or dilatation of the cardiac chambers was judged subjectively. The left ventricle was considered to be slightly hypoplastic when the cardiac apex was formed by the right ventricle, and the anterior descending coronary artery passed to the left of the apex. A left ventricular cavity approximately 1 cm in diameter was assessed as moderately hypoplastic, and a minute cavity, 0·5 cm or less, was

**TABLE 1** *Associated anomalies*

| *Case* | *Age* | *Venous anomaly* | *ASD* | *Mitral valve* | *VSD* | *Hypoplasia left ventricle* | *Pulmonary stenosis* | *Aortic stenosis* | *Persistent ductus arteriosus* |
|---|---|---|---|---|---|---|---|---|---|
| *(a) Death in first month of life* | | | | | | | | | |
| 64–355 | 1 d | — | + | Normal | + | Slight | — | + | + |
| 70–94P | 1 d | — | + | Hypo | + | Slight | — | + | + |
| 66–72 | 2 d | LSVC | SA | Normal | + | Normal | + | — | + |
| 67–83 | 2 d | TAPVD | + | Atresia | + | Moderate | — | + | + |
| 69–129 | 2 d | LSVC | + | Atresia | + | Moderate | + | — | + |
| HRGG | 3 d | — | — | Stradd | + | Slight | — | — | + |
| 51–178 | 4 d | — | — | Hypo | — | Moderate | — | — | + |
| 71–24 | 4 d | — | — | Atresia | — | Severe | — | + | + |
| 70–422P | 7 d | — | — | Atresia | + | Slight | — | + | + |
| 66–297 | 11 d | TAPVD | SA | Atresia | + | Moderate | — | — | — |
| 73–54P | 16 d | — | — | Hypo | + | Moderate | — | + | + |
| *(b) Death between 1 month and 1 year of life* | | | | | | | | | |
| 72–163P | 1 mth | — | — | Atresia | + | Severe | + | — | — |
| AGG | 1 mth | — | — | Stradd | + | Normal | — | + | + |
| 70–625P | 1 mth | — | + | Atresia | + | Severe | — | — | + |
| 70–326P | 1 mth | — | + | Atresia | — | Severe | — | — | — |
| 69–132 | 2 mth | TAPVD | + | Hypo | + | Moderate | — | — | + |
| ML | 2 mth | — | + | Atresia | + | Moderate | + | — | — |
| FFBJ | 3 mth | — | + | Atresia | + | Severe | — | — | + |
| 73–222P | 3 mth | — | — | Atresia | — | Severe | + | — | + |
| MPFB | 3 mth | — | CAVC | CAVC | CAVC | Moderate | + | — | — |
| 63–368 | 5 mth | — | + | Atresia | — | Severe | + | — | + |
| 66–48 | 5 mth | — | — | Stradd | + | Slight | + | — | — |
| 70–85 | 8 mth | LSVC | — | Atresia | — | Severe | + | — | + |
| *(c) Death after 1 year* | | | | | | | | | |
| 63–266 | 1 | — | CAVC | CAVC | CAVC | Slight | + | — | — |
| 67–246 | 3 | — | — | Normal | + | Hypertrophy | — | + | + |
| 71–99 | 4 | PAPVD | + | Stradd | + | Slight | + | — | — |
| 64–45 | 5 | — | — | Normal | + | Normal | + | — | — |

*Abbreviations:* LSVC, left superior vena cava; TAPVD, total anomalous pulmonary venous drainage; PAPVD, partial anomalous pulmonary venous drainage; ASD, atrial septal defect; SA, single atrium; CAVC, common atrioventricular canal; VSD, ventricular septal defect; PDA, persistent ductus arteriosus. +, defect present; —, defect absent; Stradd, straddling; Hypo, hypoplastic.

considered very hypoplastic. A great artery with a calibre one-third or less than the other great artery was considered to be hypoplastic. A semilunar valve with a circumference reduced by 50 per cent was considered stenotic.

In some cases, to reach a better understanding of the cardiac anatomy, the atria were separated from the ventricles and the ventricular musculature studied by blunt dissection following the planes and direction of the fibres, as described by Torrent Guasp (1966; F. Torrent Guasp, 1970, personal communication) and making serial records by drawings and photographs.

The relative position of the great arteries was noted *in situ* at the time of necropsy, and usually recorded photographically. In the few cases where this information was not available, the angiocardiographic records were used to orientate the specimen. The term normal relation of the great arteries was used when the aortic root was situated posteriorly and to the right of the pulmonary valve. We used d-lateral relation of the great arteries when both were situated at the same frontal level, the aorta being to the right. The term d-transposition was given to the cases with the aorta anterior and to the right of the pulmonary artery, regardless of the intracardiac conal anatomy.

The term crista supraventricularis was used for the curved muscular structure arching over the right ventricle. It runs from the bifurcation at the superior end of the septal band (trabecula septomarginalis) to gain the lateral wall of the ventricle. In the normal heart, it forms the posterior and inferior wall of the subpulmonary infundibulum.

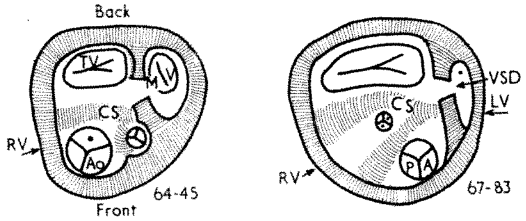

FIG. 1 *Double outlet right ventricle with double conus formed by a bifurcation of the crista supraventricularis. The conal septum is represented by the anterior branch of the crista. TV, tricuspid valve; M, mitral valve; CS, crista supraventricularis; Ao, aorta; PA, pulmonary artery (64.45 and 67.83).*

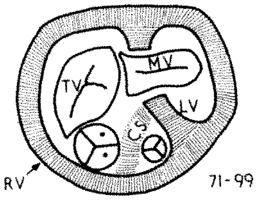

FIG. 2 *Subpulmonary conus. The aortic valve is in fibrous continuity with the tricuspid and the mitral valve straddles a ventricular septal defect (71.99).*

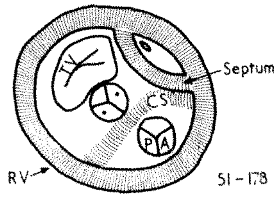

FIG. 3 *Subpulmonary conus. The crista does not originate from the interventricular septum but from the anterior ventricular wall (51.178).*

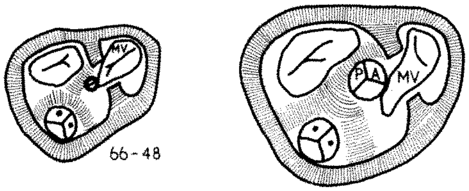

FIG. 4 *Subaortic conus. The mitral valve straddles the ventricular septal defect and is in fibrous continuity with the pulmonary valve (66.48 and HRGG).*

## Results

### Morphology of right ventricle and infundibulum

**(a) DORV with double conus (complete subaortic and subpulmonary muscular infundibula)** There were 11 cases with this anomaly (Table 2). In the 7 with normally related great vessels or d-lateral transposition the crista supraventricularis, after leaving the interventricular septum, divided into two muscular branches which formed the aortic infundibilum. The aortic valve was separated from the tricuspid by the posterior branch, and the anterior branch separated it from the pulmonary valve. The posterior arch ended in the lateral wall of the ventricle, and the anterior arch ended in the right-anterior or anterior wall (Fig. 1). The pulmonary infundibilum was formed by the initial part of the crista, its anterior branch, the anterior ventricular wall, and the anterior part of the interventricular septum. Three of the 4 cases of aortic valve stenosis fell within this group (67–83 and 64–355 with normally placed arteries and 71–24 with d-lateral transposition). In the other 4 cases of double conus there was d-transposition, with the two branches of the crista forming a pulmonary conus. Three (70–85, MPFB, and 64–65) of the 5 cases with pulmonary valve stenosis had d-transposition. Five of the 11 cases of double conus had a ventricular septal defect between the tricuspid septal leaflet and the crista supraventricularis, and two cases had a common atrioventricular canal.

**(b) DORV with a subpulmonary conus** There were 10 such cases (Fig. 2). In 7 the aortic valve was in fibrous continuity with the tricuspid valve, in 2 others it was in continuity with the tricuspid and mitral valves, and in 1 case the aortic valve was in fibrous continuity only with the mitral valve across the ventricular septal defect. The pulmonary and aortic valves were separated from each other by the crista supraventricularis. In 8 cases, the crista formed an arch similar to that in a normal heart and the trabecula septomarginalis was well defined. In the other 2 the crista supraventricularis did not touch the interventricular septum. Its medial end originated not from the septum, but from the superior portion of the anterior wall of the right ventricle, just to the right of the interventricular septum (Fig. 3). It passed posteriorly and to the right, between the valves of both great arteries, and then ran laterally reaching the anterolateral wall of the right ventricle. There was a ventricular septal defect in all but one of this group; in 6 it lay between the crista supraventricularis and the posterior-superior branch of the septal band; in 2 it lay in the area of the endocardial cushions, being straddled by the mitral valve in 1 (Fig. 2); in 1 case the ventricular septal defect was placed between both branches of the septal band (70–422P). The relation of the great arteries was normal in 7 cases and was d-lateral in 2, both with pulmonary stenosis. Case 70–422P had a hypoplastic aorta located posterior and to the left of the pulmonary artery.

**(c) DORV with a subaortic conus** There were 4 cases, all with d-transposition of the great arteries. Two (Fig. 4) showed a ventricular septal defect anterior to the septal end of the crista, underlying the pulmonary outlet. The mitral valve straddled the defect, being in fibrous continuity with the pulmonary valve. The aortic infundibulum seemed to be formed by a division of the crista supraventricularis. In the other 2 cases the pulmonary artery was hypoplastic, its valve was in fibrous continuity with the tricuspid valve, and the crista supraventricularis arose not from the septum but from the anterior ventricular wall (Fig. 5).

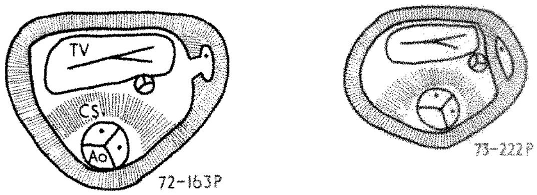

FIG. 5 *Subaortic conus. The crista is independent of the interventricular septum. Case 73-222P does not show a ventricular septal defect. Both have mitral atresia (72.163P and 73.222P).*

**(d) DORV with a common conus** In 2 cases both great arteries arose from a common infundibulum, the pulmonary and aortic valves being separated from each other by a narrow fibrous ridge (Fig. 6 and 7d). The common infundibulum resembled that of a normal right ventricle, being formed by the anterior-superior portion of the interventricular septum, the crista supraventricularis, and the anterior ventricular wall. The aortic valve and ascending aorta were hypoplastic in case 70–94P, and lay posteriorly and to the right of the pulmonary valve and artery. In Case ML, the pulmonary valve and artery were hypoplastic, lying posterior and to the left of the aorta. Both showed a ventricular septal defect between the tricuspid valve and the crista.

## Relation between great arteries

Table 2 shows this relation, together with the

TABLE 2 *Conal anatomy, valve stenosis, and relation of great arteries*

| *Case* | *Continuity of valves* | *Double conus* | *Common conus* | *Aortic stenosis* | *Pulmonary stenosis* | *Relation of great arteries* |
|---|---|---|---|---|---|---|
| 64–355 | — | + | — | + | — | Normal |
| 70–94P | — | — | + | + | — | Normal |
| 66–72 | A-T-M | — | — | — | + | Normal |
| 67–83 | — | + | — | + | — | Normal |
| 69–129 | A-T | — | — | — | + | d-lateral |
| HRGG | P-M | — | — | — | — | d-transposition |
| 51–178 | A-T | — | — | — | — | Normal |
| 71–24 | — | + | — | + | — | d-lateral |
| 70–422P | A-T | — | — | + | — | Inverted* |
| 66–297 | A-T | — | — | — | — | Normal |
| 73–54P | A-T | — | — | + | — | Normal |
| 72–163P | P-T | — | — | — | + | d-transposition |
| AGG | — | + | — | + | — | d-transposition |
| 70–625P | A-T | — | — | — | — | Normal |
| 70–326P | — | + | — | — | — | d-lateral |
| 69–132 | A-T | — | — | — | — | Normal |
| ML | — | — | + | — | + | d-transposition |
| FFBJ | — | + | — | — | — | d-lateral |
| 73–222P | P-T | — | — | — | + | d-transposition |
| MPFB | — | + | — | — | + | d-transposition |
| 63–368 | — | + | — | — | + | d-lateral |
| 66–48 | P-M | — | — | — | + | d-transposition |
| 70–85 | — | + | — | — | + | d-transposition |
| 63–266 | — | + | — | — | + | d-lateral |
| 67–246 | A-M | — | — | + | — | Normal |
| 71–99 | A-T-M | — | — | — | + | d-lateral |
| 64–45 | — | + | — | — | + | d-transposition |

*The aorta posterior and to the left of the pulmonary artery.

associated conal anatomy, and indicates whether there was semilunar valve stenosis or continuity between the atrioventricular and semilunar valves.

Out of 10 cases with a *normal relation* of the great arteries, 6 died in the first 2 weeks of life. Two had a double conus, 1 had a common conus, 1 had pulmonary stenosis, 5 had aortic stenosis, and 9 had ventricular septal defect. Among the 7 cases with *d-lateral relation* of the great arteries the age of death was variable. Five had a double conus anomaly, 4 pulmonary stenosis, and 3 a ventricular septal defect. There were 9 cases with *d-transposition* and 8 died after the first month of life. One had a common conus, 4 a double conus, 7 pulmonary stenosis, 6 a ventricular septal defect, and 1 had preductal coarctation of the aorta. One patient (70–422P) died at 7 days; the aortic valve lay behind and to the left of the pulmonary (inverted position)

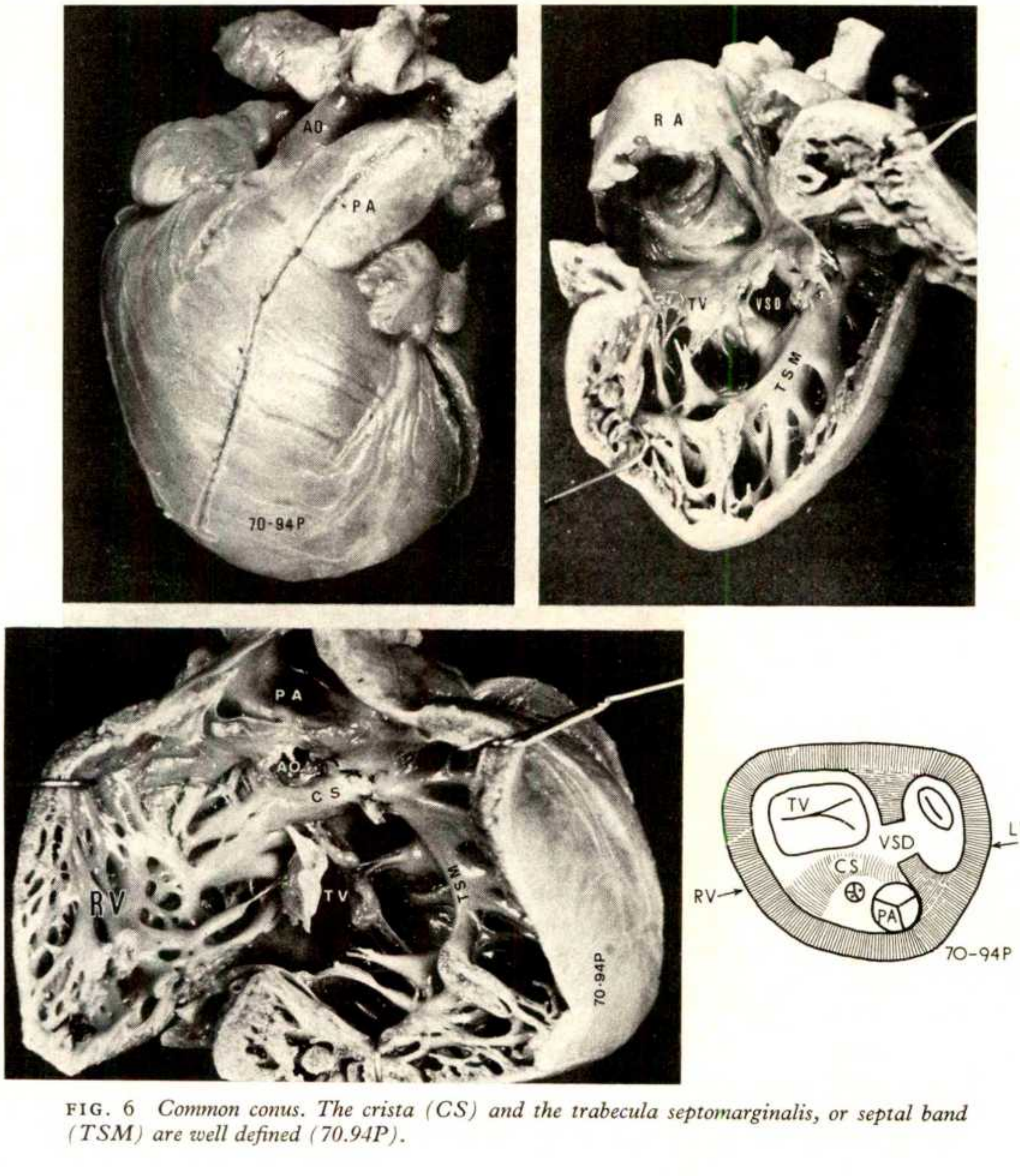

FIG. 6 *Common conus. The crista (CS) and the trabecula septomarginalis, or septal band (TSM) are well defined (70.94P).*

and there was mitral atresia with a ventricular septal defect, a displaced crista supraventricularis (not related to the septum), and hypoplasia of the aorta.

## Associated anomalies

These are listed in Table 3 and tabulated in relation to age at death in Table 1.

*A ventricular septal defect* was found in 19 specimens. In cases 66–48 and HRGG it was located within the infundibulum of the pulmonary artery; the mitral valve overrode the ventricular septal defect and was in fibrous continuity with the pulmonary artery. In Case AGG, the ventricular septal defect was placed below the pulmonary infundibulum; here again the mitral valve straddled it, but it was not in continuity with the pulmonary valve. In 2 other specimens with an anterior ventricular septal defect (70–422P and 72–163P) the crista supraventricularis formed the infundibulum for a great artery but was not related to the interventricular septum, as described previously (see Fig. 5). In 10 cases the ventricular septal defect was located between the septal leaflet of the tricuspid valve and the crista supraventricularis. In another 2 cases (66–72 and 71–99) the ventricular septal defect lay in the area of the endocardial cushions. In both, the mitral and tricuspid valves were in fibrous continuity. Two of the cases (HRGG, AGG), with a ventricular septal defect overridden by the mitral valve, were included in a previous publication (Quero Jimenez *et al.*, 1973).

*A left superior vena cava* was present in 3 cases, all with pulmonary stenosis.

*Anomalous pulmonary venous drainage* was seen in 4 cases. The veins drained via the coronary sinus (2), directly into the right atrium (1), and the other showed partial drainage of the right pulmonary veins into the right atrium. All had a ventricular septal defect, none had pulmonary stenosis, and the relation of semilunar valves was normal.

TABLE 3 *Associated anomalies*

| *Anomaly* | *No. of cases* |
|---|---|
| Left superior vena cava | 3 |
| Anomalous pulmonary venous drainage | 4 |
| Juxtaposition of atrial appendages | 1 |
| Single atrium | 2 |
| Atrial septal defect | 10 |
| Common atrioventricular canal | 2 |
| Mitral atresia | 13 |
| Straddling mitral valve | 4 |
| Ventricular septal defect | 19 |
| Pulmonary stenosis | 12 |
| Aortic stenosis | 8 |
| Persistent ductus arteriosus | 18 |
| Right aortic arch | 1 |
| Exomphalos with cardiac diverticulum | 1 |

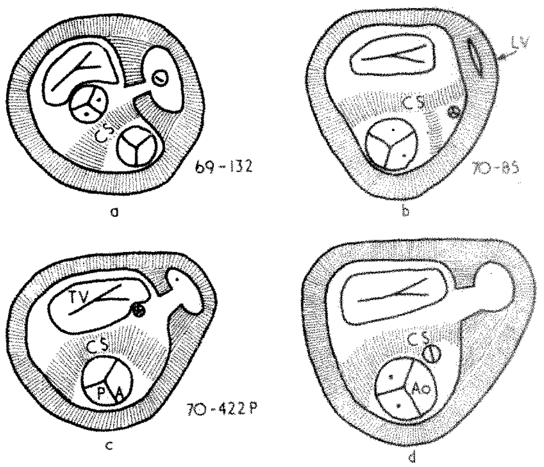

FIG. 7 *Four different patterns of conal anatomy. (a) Subpulmonary conus, the crista separates the semilunar valves. (b) The conal septum is represented by the anterior branch of the crista. (c) The crista does not originate from the septum but from the anterior ventricular wall, and separates the semilunar valves. (d) The crista lies behind the semilunar valves and there is no conal septum (69.132, 70.85, 70.422P, and ML).*

*An atrial septal defect* was encountered in 10 cases: ostium secundum in 9 and ostium primum in 1.

*A single atrium* was found in 2 specimens. One (66–297, Fig. 8) had a very large right atrium without any trace of a left atrium, left atrial appendage, or mitral valve. Both cases had anomalous pulmonary venous drainage, a ventricular septal defect, a subpulmonary conus, and normal relation of the great arteries. Both died during the first two weeks of life. The other 25 cases showed right atrial enlargement. There were single cases with absence of the coronary sinus (FFBJ), absence of the left atrial appendage (70–625P), and left juxtaposition of the atrial appendages (63–266). The foramen ovale was not identifiable in 2 specimens. The left atrium was normal in 8, hypertrophied in 2, and hypoplastic in 15 cases.

*Mitral atresia* was encountered in 13 cases; it was associated with an atrial septal defect in 7, a ventricular septal defect in 8, a double conus anomaly in 6, and pulmonary stenosis in 6. *The left ventricle* was underdeveloped in 24 cases. The 9 cases with a very hypoplastic left ventricle had mitral atresia without a ventricular septal defect,

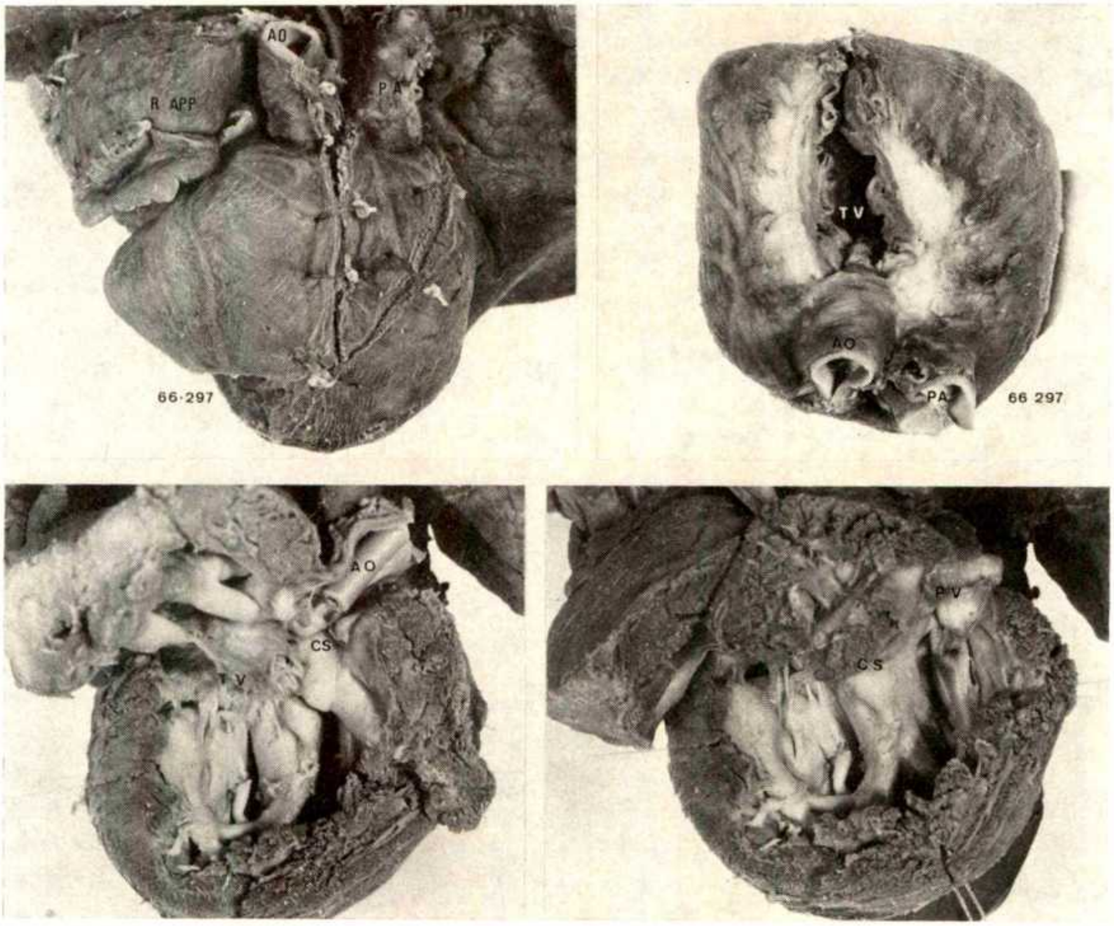

FIG. 8 *Case 66–297. The left atrium is completely absent. Note how the anterior leaflet of the tricuspid valve attaches some chordae tendineae to the crista supraventricularis. RAPP = right atrial appendage.*

*Aortic valve stenosis* was seen in 8 instances and was associated with infundibular stenosis (1 case), hypoplastic ascending aorta (3), hypoplastic aortic arch (2), and preductal coarctation (2). *A biventricular diverticulum*, which extended into an exomphalos, was present in Case 66–72 and was associated with a large ventricular septal defect, a single atrium, and a narrow tricuspid valve.

### Discussion

Analysis of the findings in these 27 cases of DORV shows that none was free from serious associated malformations. This is perhaps not surprising in a necropsy study. Comparable data from successfully treated cases would be complementary and enable a comprehensive study of the full range of this condition to be presented.

The commonest association was with ventricular septal defect (19 cases), and in DORV this constitutes the only outlet from the left ventricle. Eleven of these had significant defects of the atrial septum and in addition there were 2 cases of common atrioventricular canal. Nine had pulmonary stenosis, 7 had aortic stenosis, and 8 had mitral atresia. DORV with ventricular septal defect and no other significant anomaly is the most suitable combination for surgical correction, if this can be performed before the onset of irreversible hypertensive arteriopathic changes in the lung vessels, but there were no such examples in this series.

Pulmonary stenosis (12 cases) was the next commonest associated finding and was particularly frequent in the older children. It was observed in 8 of the 10 children of 3 months of age or older, but in only 4 of the 17 younger patients. Aortic stenosis, by contrast, was commoner in the younger group (7/17 and 1/10). In all but 1 of the 8 cases of aortic stenosis there was hypoplasia of the left ventricle and usually stenosis or atresia of the mitral valve.

A persistent ductus was seen in 18 cases. This was particularly common in the younger children as might be expected, not only because of the age effect, but because of the frequency of aortic stenosis in these babies. There was a persistent ductus arteriosus in 5 of the 10 children of 3 months of age or more, and in only 1 of the 4 who died after the age of 12 months.

Anomalous pulmonary venous drainage was found in 4 patients; 2 had mitral atresia and all had a ventricular septal defect. There were 3 patients with bilateral superior venae cavae; all 3 had pulmonary stenosis and 2 had mitral atresia.

These various findings underline the importance of the associated anomalies, and indicate that particular attention should be directed to the possibility of aortic, mitral, or pulmonary stenosis before surgical correction is undertaken. Anomalous pulmonary venous drainage should also be excluded. In addition, it would be desirable to assess the location of the ventricular septal defect.

The morphology of the infundibular region is of considerable practical importance in relation to diagnosis and to surgical treatment. The interpretation of the findings also has a bearing on our understanding of the normal development of the heart with particular reference to the crista supraventricularis and conal septum. The latter is the muscular tissue which normally separates the two semilunar valves and it normally contributes to the formation of the anterior part of the ventricular septum.

A complete muscular aortic infundibulum (Fig. 4 and 5) is usually associated with pulmonary stenosis, ventricular septal defect, and d-transposition (Table 4). The mitral valve, if it is not stenotic, tends to straddle the ventricular septal defect. The crista supraventricularis is dissociated from the anterior part of the ventricular septum and forms a conal septum by passing between the two semilunar valves (Fig. 5) or by giving rise to an anterior branch (Fig. 4).

A double conus (Fig. 1) is commonly associated with either pulmonary or aortic stenosis (Table 2). The aorta usually is in either the d-lateral or the d-transposition situation (Table 4) and the posterior valve tends to be stenosed. The crista supraventricularis forms the posterior wall of the conus and its anterior branch forms a conal septum.

TABLE 4 *Relation of conal anatomy and semilunar valve stenosis to position of great arteries*

| | *Normal* | *d-lateral* | *d-transposition* | *Total* |
|---|---|---|---|---|
| Subaortic conus | 0 | 0 | 4 | 4 |
| Subpulmonary conus | 7+1* | 2 | 0 | 10 |
| Double conus | 2 | 5 | 4 | 11 |
| Common conus | 1 | 0 | 1 | 2 |
| Aortic stenosis | 5+1* | 1 | 1 | 8 |
| Pulmonary stenosis | 1 | 4 | 7 | 12 |
| No stenosis | 4 | 2 | 1 | 7 |
| Total | 10+1* | 7 | 9 | |

*1 case with inversion of aorta.

A common conus, enclosing the origin of both major vessels with no intervening muscular elements, was seen only twice (Table 2, Fig. 6 and 7d). There was no conal septum between the two valves, but the crista supraventricularis was well developed and formed the posterior wall of the conus.

In the 10 cases of DORV with a subpulmonary conus (Fig. 2, 3, and 7c) the crista formed a conal septum between the two semilunar valves. It usually formed an arch of normal appearance with a well-defined trabecular septomarginalis and a ventricular septal defect was common. In 2 cases (Fig. 3 and 7c) the crista did not fuse with the ventricular septum.

The variations in the infundibular morphology in DORV suggest that the crista develops normally, not from the left anterior conal ridge as commonly understood, but from the bulbus cordis. The four main patterns observed are shown in Fig. 7. They show that the crista is always represented even though the conal septum may be absent. This independence may indicate different origins—the conal septum from the conal ridges and the crista from the bulbus.

The pattern seen in our 2 cases with a common conus appears to be related to that in common truncus arteriosus. Case 70–94P (Fig. 6) was very similar to that described by Van Praagh and Van Praagh (1965) as common truncus with persistence of the VIth arch. It showed complete truncal septation, but Van Praagh's lacked septation in its lowest portion. Case ML (Fig. 7d) showed a similar relation to common truncus with persistence of the IVth arch, and fibrous discontinuity between the truncal and the atrioventricular valves.

The conal anatomy is related to the position and calibre of the great arteries. Table 4 shows that the anterior vessel always has a muscular conus, though

TABLE 5 *Relation of conal anatomy and semilunar valve stenosis*

| *Conus* | *Stenosis* | | | *Total* |
|---|---|---|---|---|
| | *Nil* | *Pulmonary* | *Aortic* | |
| Subaortic | 1 | 3 | 0 | 4 |
| Subpulmonary | 4 | 3 | 3 | 10 |
| Double | 2 | 5 | 4 | 11 |
| Common | 0 | 1 | 1 | 2 |
| Total | 7 | 12 | 8 | |

in some cases this is part of a common or double conus. Looked at another way, it is clear that normal position of the great vessels is usually associated with a pulmonary conus, but d-lateral, and to a lesser degree d-transposition, tend to be associated with a double conus. Table 5 shows that a stenotic outlet is usually related to the posterior vessel. In other words, normal relation of the two arteries usually implies a single pulmonary conus with or without aortic stenosis, and in d-transposition there is usually a double or single aortic conus with pulmonary stenosis.

Our 2 cases with a common atrioventricular canal both had a double conus with pulmonary stenosis but this cannot be said to establish a consistent pattern.

From the clinical point of view, 12 of our cases had features of Fallot's tetralogy and 7 showed the picture of a large ventricular septal defect, both being well recognized modes of presentation in DORV (Neufeld *et al.*, 1961a, b). More than a third of our cases, however, died within the first 2 weeks of life, with the predominant clinical features of hypoplastic left ventricle and aortic stenosis.

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# Test of reliability of echocardiographic estimation of left ventricular dimensions and volumes

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*This test is based on the incompressibility of myocardium, which dictates that left ventricular wall volume remains constant throughout the cardiac cycle.*

*The volumes occupied by the left ventricular cavity, by ventricular wall plus cavity, and hence by ventricular wall alone were estimated, both at end-systole and at end-diastole, from echocardiographic measurements of cavity transverse dimension and wall thickness. Wall volumes were determined by assuming an ellipsoid shape (the major axis being predicted from regression equations relating angiocardiographic and echocardiographic cavity dimensions) and also by the cube method. A discrepancy between systolic and diastolic wall volume estimates indicates either that the measurements of ventricular dimensions were unreliable or that the assumptions of ventricular geometry involved in the volume calculations were incorrect.*

*Studies were made on 60 subjects. Using the ellipsoid formula, values for wall volume ranged from 66 to 719 ml; systolic and diastolic wall volumes correlated closely (*$r=0{\cdot}96$*, mean difference*$=6{\cdot}8\pm0{\cdot}9$ *(SEM) %) supporting the reliability of the echocardiographic dimensions and estimates of cavity and wall volume. In the 12 patients with very large end-diastolic cavity transverse dimensions (6·5 to 8·6 cm) however, correlation was less good (*$r=0{\cdot}81$*, mean difference*$=14{\cdot}3\pm2{\cdot}3$ *(SEM) %). Using the cube method, which does not allow for the changing relation between minor and major cavity axes with increasing cavity size, wall volumes were greater (76 to 986 ml) but correlation was similar (*$r=0{\cdot}94$*, mean difference*$=7{\cdot}1\pm0{\cdot}9$ *(SEM) %).*

*Having established that it is possible to obtain close agreement between wall volumes determined at different points in the cardiac cycle, this test can be used to assess the reliability of echocardiographic left ventricular dimensions and volume estimates in individual subjects.*

The noninvasive technique of echocardiography can be used to estimate several indices of left ventricular function including stroke volume, ejection fraction, ventricular mass, and wall stress. There are two main problems in the echocardiographic assessment of left ventricular function. The first problem is the difficulty which can be encountered in the recording and in the correct interpretation of left ventricular echocardiograms. The second problem lies in the fact that the estimation of left ventricular volumes is based on the measurement of a single cavity dimension and it, therefore, necessarily involves several assumptions as to the shape of the left ventricle. Though these assumptions are supported by angiocardiographic observations (Greene *et al.*, 1967; Sandler and Dodge, 1968; Gault, Ross, and Braunwald, 1968), the estimation of a three-dimensional shape from a single dimension is clearly open to criticism, particularly in patients with pronounced left ventricular cavity enlargement, where the cavity tends to be spherical rather than ellipsoid (Fortuin *et al.*, 1971; Gibson, 1973), and in patients with an irregular or atypical cavity shape, as may occur in hypertrophic cardiomyopathy and ischaemic heart disease (Gibson, 1973; Feigenbaum, 1975).

We tested the reliability of the information which can be derived from the left ventricular echocardiogram, on a within-patient basis, by comparing diastolic and systolic estimates of left ventricular wall volume. The left ventricular wall, being non-gaseous, is incompressible and thus left ventricular wall volume must remain constant

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throughout the cardiac cycle. Wall volume can be estimated from echocardiographic measurements of wall thickness and cavity transverse dimension. Measurement of these two ventricular dimensions, and hence estimates of wall volume, can be made at end-diastole, when wall thickness is at a minimum and cavity size is at a maximum, and also at end-systole, when wall thickness is at a maximum and cavity size is at a minimum. If the ventricular dimensions are reliable, and if the assumptions of ventricular geometry involved in echocardiographic estimation of left ventricular volumes are correct, then diastolic and systolic estimates of wall volume should agree. Lack of agreement indicates either that the ventricular dimensions or geometric assumptions are unreliable, or that the echocardiogram is technically unsatisfactory or has been misinterpreted.

## Subjects and methods

Left ventricular echocardiograms obtained from 8 normal subjects and from 52 patients with disorders likely to cause left ventricular enlargement were studied. The echocardiograms were selected for their clarity; in all records it was possible unequivocally to identify left ventricular endocardium and epicardium.

The echocardiograms were recorded by the standard method (Feigenbaum, 1972) on light sensitive paper (Kodak Linagraph, 1895), at a paper speed of 50 mm/s, using a Smith Kline 20A ultrasonoscope, 2·25 MHz 10 cm focussed transducer, and a Honeywell 1856 strip chart recorder. End-diastolic (Dd) and end-systolic (Ds) cavity transverse dimension, and end-diastolic (Wd) and end-systolic (Ws) left ventricular wall thicknesses were measured with the aid of the simultaneously recorded calibration scale (Fig. 1). Cavity transverse dimension was measured as the distance between left ventricular septal and posterior wall endocardium. Wall thickness was measured as the distance between posterior wall endocardium and epicardium. End-diastole was defined as the time of onset of the QRS complex of the simultaneously recorded electrocardiogram, and end-systole as the point of maximum anterior movement of the posterior wall.

Left ventricular wall volumes were calculated, at end-diastole and end-systole, by subtracting the estimated cavity volume from the estimated volume occupied by ventricular wall plus cavity. Two different formulae were used.

### (1) Cube formula

This formula is based on the empirical observation that the cube of the cavity transverse dimension ($D^3$) approximates to the left ventricular cavity volume (Feigenbaum *et al.*, 1969). By assuming uniform wall thickness (W), the volumes occupied by ventricular wall plus cavity ($(2W+D)^3$) and hence by ventricular wall alone can be calculated, thus: wall volume $=(2W+D)^3—D^3$ (Bennett and Evans, 1974).

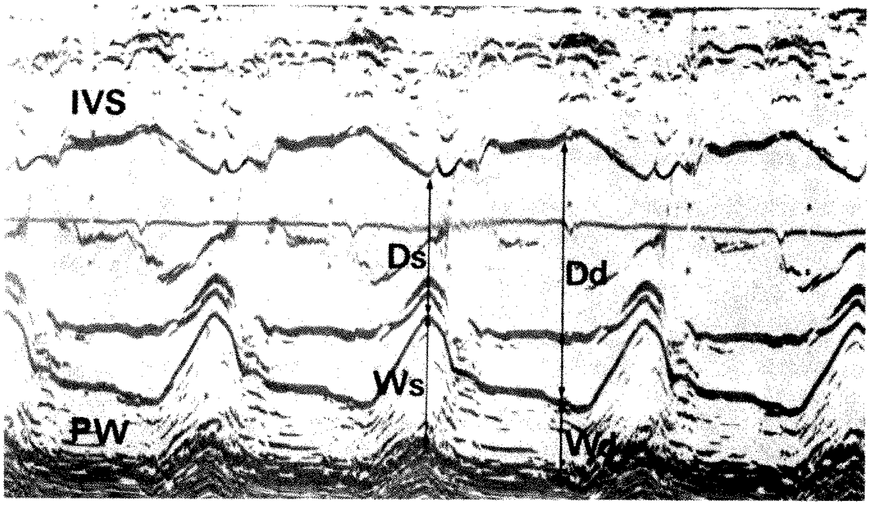

FIG. 1 *Left ventricular echocardiogram (Case 26). IVS, interventricular septum; PW, posterior wall; Ws and Wd, end-systolic and end-diastolic wall thickness respectively; Ds and Dd, end-systolic and end-diastolic cavity transverse dimension, respectively.*

### (2) Ellipsoid formula

The empirical observation on the relation of the cube of the cavity transverse dimension to cavity volume can be explained by assuming (a) that the left ventricle has the shape of an ellipsoid of revolution, a widely held assumption in angiocardiographic work (Dodge *et al.*, 1966; Greene *et al.*, 1967; Sandler and Dodge, 1968), and (b) that the cavity transverse dimension is equal to each minor axis and to the semi-major axis (Chapelle and Mensch, 1969; Popp and Harrison, 1970; Troy, Pombo, and Rackley, 1972). If these relations hold, the minor radii are each D/2 and the major axis is D, and the cavity volume becomes $4/3\ \pi\ (D/2)^2D = 1\cdot047D^3, \simeq D^3$.

However, with cavity dilatation, the cavity minor axis increases relative to the major axis, the ventricle becoming more spherical in shape (Fortuin *et al.*, 1971; Teichholz *et al.*, 1972; Gibson, 1973). In addition, the relation between major and minor axes varies during the cardiac cycle (Gault *et al.*, 1968). Gibson (1973), in a study of 50 patients with a variety of cardiac disorders, derived regression equations relating angiocardiographic measurements of cavity major axis (L) to echocardiographic measurements of cavity transverse dimension (D), at end-diastole and end-systole:

$$Ld = 5\cdot90 + 0\cdot98\ Dd;\ Ls = 4\cdot18 + 1\cdot14\ Ds.$$

These regression equations are similar to that derived from end-diastolic data by Ratshin, Rackley, and Russell (1974):

$$Ld/2 = 2\cdot518 + 0\cdot462Dd.$$

By predicting the cavity major axis from Gibson's regression equations, left ventricular wall volume can be estimated, in the same way as angiocardiographic measurements are made (Rackley *et al.*, 1964), by using the formula for the volume of an ellipsoid. Thus: wall volume =

$$4/3\ \pi\ (W+D/2)^2(W+L/2) - 4/3\ \pi\ (D/2)^2L/2.$$

Correlation was sought between end-diastolic and end-systolic wall volume estimates, and the difference between these estimates was expressed as a percentage of the diastolic wall volume estimate. The subjects' clinical details, ventricular dimensions, and wall volume estimates are given in Table 1.

TABLE 1 *Diagnoses, systolic and diastolic ventricular dimensions, and wall volumes*

| *Case No.* | *Diagnosis* | *Age (y)* | *s/d* | *W(cm)* | *D(cm)* | *L(cm)* | *Wall volume (ml)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Cube* | *Ellipsoid* |
| 1 | Normal | 29 | s | 1·55 | 3·30 | 7·95 | 226 | 192 |
| | | | d | 0·90 | 5·35 | 11·15 | 212 | 180 |
| 2 | Normal | 38 | s | 1·35 | 2·80 | 7·50 | 144 | 131 |
| | | | d | 0·85 | 4·45 | 10·25 | 145 | 130 |
| 3 | Normal | 25 | s | 1·50 | 3·10 | 7·70 | 197 | 170 |
| | | | d | 0·95 | 4·85 | 10·65 | 194 | 168 |
| 4 | Normal | 27 | s | 1·55 | 2·45 | 6·95 | 156 | 140 |
| | | | d | 1·10 | 3·70 | 9·55 | 155 | 146 |
| 5 | Normal | 25 | s | 1·55 | 3·10 | 7·70 | 213 | 186 |
| | | | d | 0·95 | 4·80 | 10·60 | 190 | 166 |
| 6 | Normal | 20 | s | 1·45 | 2·70 | 7·25 | 156 | 139 |
| | | | d | 0·95 | 3·90 | 9·70 | 136 | 127 |
| 7 | Normal | 18 | s | 1·35 | 3·30 | 7·95 | 180 | 155 |
| | | | d | 0·95 | 4·65 | 10·45 | 181 | 159 |
| 8 | Normal | 18 | s | 1·50 | 3·15 | 7·75 | 201 | 173 |
| | | | d | 0·95 | 5·00 | 10·80 | 204 | 175 |
| 9 | Coarct | 30 | s | 1·95 | 2·75 | 7·30 | 273 | 230 |
| | | | d | 1·25 | 4·60 | 10·40 | 261 | 231 |
| 10 | Coarct | 31 | s | 2·00 | 3·05 | 7·65 | 322 | 266 |
| | | | d | 1·05 | 6·00 | 11·80 | 315 | 255 |
| 11 | Coarct | 20 | s | 2·40 | 3·05 | 7·65 | 455 | 377 |
| | | | d | 1·55 | 5·35 | 11·15 | 450 | 366 |
| 12 | Coarct | 17 | s | 2·20 | 3·00 | 7·60 | 378 | 308 |
| | | | d | 1·30 | 5·20 | 11·00 | 334 | 278 |
| 13 | Coarct | 20 | s | 2·05 | 3·15 | 7·75 | 350 | 286 |
| | | | d | 1·40 | 5·15 | 10·95 | 366 | 303 |
| 14 | Coarct | 17 | s | 2·30 | 3·00 | 7·60 | 412 | 333 |
| | | | d | 1·45 | 5·00 | 10·80 | 368 | 306 |
| 15 | Coarct | 20 | s | 2·40 | 3·05 | 7·65 | 455 | 377 |
| | | | d | 1·55 | 5·35 | 11·15 | 450 | 366 |

*Continued*

TABLE 1 *continued*

| *Case No.* | *Diagnosis* | *Age (y)* | *s/d* | *W(cm)* | *D(cm)* | *L(cm)* | *Wall volume (ml)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Cube* | *Ellipsoid* |
| 16 | Hypert | 53 | s | 2·50 | 2·70 | 7·30 | 437 | 416 |
| | | | d | 1·70 | 4·90 | 10·70 | 454 | 374 |
| 17 | Hypert | 40 | s | 2·60 | 3·00 | 7·60 | 524 | 415 |
| | | | d | 1·90 | 5·00 | 10·80 | 557 | 451 |
| 18 | Hypert | 30 | s | 2·05 | 3·00 | 7·60 | 331 | 273 |
| | | | d | 1·45 | 4·75 | 10·55 | 341 | 288 |
| 19 | AS | 43 | s | 1·90 | 1·85 | 6·30 | 174 | 157 |
| | | | d | 1·20 | 3·65 | 9·50 | 173 | 162 |
| 20 | AS | 33 | s | 2·10 | 2·00 | 6·50 | 230 | 202 |
| | | | d | 1·30 | 3·70 | 9·50 | 199 | 183 |
| 21 | AS | 30 | s | 1·70 | 2·70 | 7·25 | 207 | 187 |
| | | | d | 1·10 | 4·10 | 9·90 | 181 | 152 |
| 22 | AS | 19 | s | 1·70 | 3·15 | 7·75 | 250 | 210 |
| | | | d | 1·10 | 5·00 | 10·80 | 248 | 212 |
| 23 | AS | 44 | s | 2·00 | 2·90 | 7·50 | 304 | 254 |
| | | | d | 1·50 | 4·10 | 9·90 | 289 | 253 |
| 24 | AS | 52 | s | 2·00 | 2·20 | 6·70 | 228 | 198 |
| | | | d | 1·30 | 4·00 | 9·80 | 223 | 201 |
| 25 | AS | 58 | s | 2·30 | 2·35 | 6·85 | 323 | 270 |
| | | | d | 1·60 | 4·25 | 10·05 | 337 | 290 |
| 26 | AS | 18 | s | 2·05 | 2·15 | 6·65 | 234 | 205 |
| | | | d | 1·35 | 4·05 | 9·85 | 241 | 215 |
| 27 | AS | 19 | s | 1·75 | 1·85 | 6·30 | 147 | 134 |
| | | | d | 1·20 | 3·35 | 9·15 | 153 | 147 |
| 28 | AS | 43 | s | 1·90 | 1·85 | 6·30 | 174 | 157 |
| | | | d | 1·20 | 3·65 | 9·50 | 173 | 162 |
| 29 | AS, LVF | 58 | s | 1·90 | 7·20 | 12·40 | 958 | 690 |
| | | | d | 1·35 | 8·30 | 14·05 | 759 | 554 |
| 30 | AS, AR | 45 | s | 2·20 | 2·60 | 7·10 | 325 | 270 |
| | | | d | 1·40 | 4·65 | 10·45 | 313 | 269 |
| 31 | AS, AR | 47 | s | 2·60 | 3·10 | 7·70 | 542 | 427 |
| | | | d | 1·70 | 5·60 | 11·40 | 553 | 440 |
| 32 | AS, AR | 50 | s | 3·00 | 3·00 | 7·60 | 710 | 541 |
| | | | d | 2·30 | 4·80 | 10·60 | 720 | 575 |
| 33 | AS, AR | 52 | s | 1·55 | 4·50 | 9·30 | 348 | 276 |
| | | | d | 1·25 | 5·70 | 11·50 | 366 | 297 |
| 34 | AS, AR | 30 | s | 2·80 | 3·60 | 8·30 | 736 | 560 |
| | | | d | 1·80 | 5·90 | 11·70 | 652 | 510 |
| 35 | AS, AR | 36 | s | 2·15 | 2·65 | 7·20 | 317 | 264 |
| | | | d | 1·50 | 5·00 | 10·80 | 387 | 321 |
| 36 | AS, AR | 19 | s | 1·80 | 3·50 | 8·15 | 315 | 258 |
| | | | d | 1·30 | 5·00 | 10·80 | 314 | 264 |
| 37 | AS, AR, MS | 57 | s | 2·15 | 2·45 | 6·95 | 293 | 247 |
| | | | d | 1·50 | 4·25 | 10·05 | 304 | 264 |
| 38 | AS, AR, MS | 46 | s | 1·80 | 2·05 | 6·50 | 172 | 151 |
| | | | d | 1·05 | 4·05 | 9·85 | 166 | 152 |
| 39 | CAF | 26 | s | 1·85 | 3·65 | 8·35 | 348 | 270 |
| | | | d | 1·15 | 5·65 | 11·45 | 322 | 264 |
| 40 | AR | 27 | s | 1·90 | 3·45 | 8·10 | 340 | 277 |
| | | | d | 1·10 | 6·10 | 11·90 | 345 | 277 |
| 41 | AR | 19 | s | 2·05 | 4·95 | 9·80 | 620 | 470 |
| | | | d | 1·35 | 7·65 | 13·40 | 661 | 492 |
| 42 | AR | 46 | s | 2·25 | 4·90 | 9·75 | 713 | 537 |
| | | | d | 1·40 | 7·50 | 13·25 | 671 | 501 |
| 43 | AR | 37 | s | 1·60 | 3·60 | 8·30 | 268 | 222 |
| | | | d | 1·00 | 5·60 | 11·40 | 263 | 216 |
| 44 | AR | 6 | s | 1·00 | 2·50 | 7·05 | 76 | 66 |
| | | | d | 0·65 | 3·50 | 9·35 | 68 | 69 |
| 45 | AR | 32 | s | 2·15 | 3·70 | 8·40 | 461 | 365 |
| | | | d | 1·05 | 6·80 | 12·60 | 391 | 305 |
| 46 | AR | 56 | s | 1·85 | 5·90 | 10·90 | 679 | 506 |
| | | | d | 1·55 | 7·35 | 13·10 | 744 | 556 |

*Continued*

TABLE 1 *continued*

| *Case No.* | *Diagnosis* | *Age (y)* | *s/d* | *W(cm)* | *D(cm)* | *L(cm)* | *Wall volume (ml)* *Cube* | *Ellipsoid* |
|---|---|---|---|---|---|---|---|---|
| 47 | AR, MR | 19 | s | 1·90 | 4·70 | 9·55 | 510 | 395 |
| | | | d | 1·30 | 6·60 | 12·35 | 491 | 381 |
| 48 | AR, VSD | 23 | s | 2·35 | 5·90 | 10·90 | 986 | 719 |
| | | | d | 1·45 | 8·55 | 14·30 | 876 | 633 |
| 49 | AR, VSD | 17 | s | 2·00 | 4·20 | 9·00 | 477 | 375 |
| | | | d | 1·10 | 6·50 | 12·50 | 384 | 306 |
| 50 | AR, MS | 43 | s | 1·75 | 4·55 | 9·35 | 428 | 335 |
| | | | d | 1·25 | 6·40 | 12·15 | 443 | 347 |
| 51 | AVR | 50 | s | 1·90 | 4·30 | 9·10 | 452 | 355 |
| | | | d | 1·10 | 6·80 | 12·60 | 415 | 323 |
| 52 | AVR | 32 | s | 2·00 | 2·35 | 6·85 | 243 | 209 |
| | | | d | 1·30 | 4·30 | 10·10 | 249 | 219 |
| 53 | MR | 23 | s | 2·00 | 5·00 | 9·90 | 604 | 460 |
| | | | d | 1·05 | 7·80 | 13·55 | 496 | 372 |
| 54 | MR | 52 | s | 2·00 | 5·25 | 10·15 | 647 | 487 |
| | | | d | 1·55 | 8·10 | 13·85 | 874 | 638 |
| 55 | MR | 51 | s | 1·95 | 3·45 | 8·10 | 356 | 289 |
| | | | d | 1·20 | 5·70 | 11·50 | 346 | 282 |
| 56 | MR | 30 | s | 1·95 | 3·00 | 7·60 | 302 | 251 |
| | | | d | 1·10 | 5·65 | 11·45 | 303 | 249 |
| 57 | MR, MS | 51 | s | 1·55 | 3·70 | 8·40 | 264 | 218 |
| | | | d | 1·00 | 5·55 | 11·35 | 259 | 215 |
| 58 | PDA | 10 | s | 1·05 | 3·00 | 7·60 | 106 | 96 |
| | | | d | 0·60 | 4·70 | 10·50 | 102 | 92 |
| 59 | PDA | 16 | s | 1·45 | 4·25 | 9·05 | 289 | 234 |
| | | | d | 0·95 | 5·70 | 11·50 | 254 | 210 |
| 60 | COCM | 42 | s | 1·55 | 6·15 | 11·20 | 559 | 569 |
| | | | d | 1·00 | 7·50 | 13·25 | 435 | 522 |

s=end-systolic data; d=end-diastolic data; W=wall thickness; D=cavity transverse dimension; L=estimated major axis; Coarct=aortic coarctation; hypert=essential hypertension; AS=aortic stenosis; AR=aortic regurgitation; MS=mitral stenosis; MR=mitral regurgitation; CAF=coronary artery fistula; VSD=ventricular septal defect; AVR=leaking aortic prosthesis; PDA=persistent ductus arteriosus; COCM=congestive cardiomyopathy.

## Results

Overall, there was close correlation between diastolic and systolic wall volume estimates using both the cube formula and the ellipsoid formula (Table 2). In some of the patients however, mainly those with pronounced cavity enlargement, agreement was poor. An example is shown in Fig. 2.

In subjects with normal or moderately enlarged cavities, wall volumes determined using the cube formula were slightly greater than those determined using the ellipsoid formula. In patients with very large cavities, where the predicted major axis was substantially less than twice the minor axis, wall volumes calculated using the cube formula were much greater than those determined from the ellipsoid formula.

## Discussion

In most cases there was close agreement between estimates of left ventricular wall volume at end-systole, when wall thickness is at a maximum and cavity size is at a minimum, and at end-diastole, when wall thickness is at a minimum and cavity size is at a maximum. This supports the reliability of the wall thickness and cavity dimension measurements, and of the assumptions involved in the volume determinations. The agreement does not *establish* the reliability of the measurements, but it is certainly consistent with it, and lack of agreement is certainly inconsistent with reliability. In some cases, mainly those with very large ventricular cavities, agreement was poor indicating in these cases, either that the measurements of ventricular dimensions were unreliable or that the assumptions of ventricular geometry involved in the volume calculations could not be applied.

Though agreement was not improved by use of the method based on the ellipsoid formula, we feel that this method is likely to yield more realistic estimates of wall volume since it does take into account the changing relation between major and minor axes which occurs during the cardiac cycle and with increasing cavity size, whereas the cube method is based on a fixed relation between the two axes.

The test is based on the constancy of ventricular wall volume throughout the cardiac cycle. It might

TABLE 2 *Comparison of systolic and diastolic wall volume estimates*

| | *C/E* | *n* | *r* | *P<* | *Mean difference (%)* |
|---|---|---|---|---|---|
| All subjects | C | 60 | 0·94 | 0·001 | 7·1 ± 0·9 (SEM) |
| | E | | 0·96 | 0·001 | 6·8 ± 0·9 (SEM) |
| Subjects with Dd ≥ 6·5 cm | C | 12 | 0·82 | 0·001 | 15·9 ± 2·6 (SEM) |
| | E | | 0·81 | 0·001 | 14·3 ± 2·3 (SEM) |
| Subjects with Dd < 6·5 cm | C | 48 | 0·99 | 0·001 | 4·8 ± 0·7 (SEM) |
| | E | | 0·98 | 0·001 | 4·9 ± 0·7 (SEM) |

C and E = wall volumes estimated by cube and ellipsoid formulae respectively; Dd = end-diastolic cavity transverse dimension; n = number of subjects; r = correlation coefficient; P = significance level; SEM = standard error of mean.

be argued that a change in wall volume could occur as a result of expulsion of blood from the myocardium during systole. Assuming a myocardial blood flow of 66 ml/min per 100 g (Brachfeld, Bozer, and Gorlin, 1959), i.e. approximately 1 ml/s per 100 g, and using a mean transit time for the coronary circulation of 7 seconds (Gorlin, 1960), the coronary blood volume is calculated to be 7·0 ml/100 g. If the myocardium were completely emptied of blood during systole, it would only account for a 7 per cent change in wall volume. It is extremely unlikely that the myocardium is completely emptied of blood in systole. An assessment of the volume of blood likely to be expelled from the myocardium in systole can be obtained by a consideration of the total coronary flow. Using the above estimate for myocardial blood flow and assuming a heart rate of 60/minute, only approximately 1 ml blood/min per 100 g of myocardium can be expelled. Even if all this flow occurred between end-diastole and end-systole, it could only constitute 1 ml blood volume to 100 g myocardial tissue or approximately 1 per cent. In view of the range of heart rates possible and the uncertain apportioning of blood between the left and right ventricular myocardium, it seems best to assume simply that any myocardial volume change related to expulsion of blood will account for between 1 and 7 per cent and will probably be much closer to the former than the latter.

Comparison of systolic and diastolic wall volume estimates has been used in angiocardiographic studies to assess the reliability of wall thickness and cavity volume measurements (Hugenholtz, Kaplan, and Hull, 1969; Lewis and Sandler, 1971). A difference of up to 25 per cent is usually regarded as acceptable (Lewis and Sandler, 1971; Sandler and Alderman, 1974). Agreement between wall volume estimates in this echocardiographic study was closer probably because of the tendency to

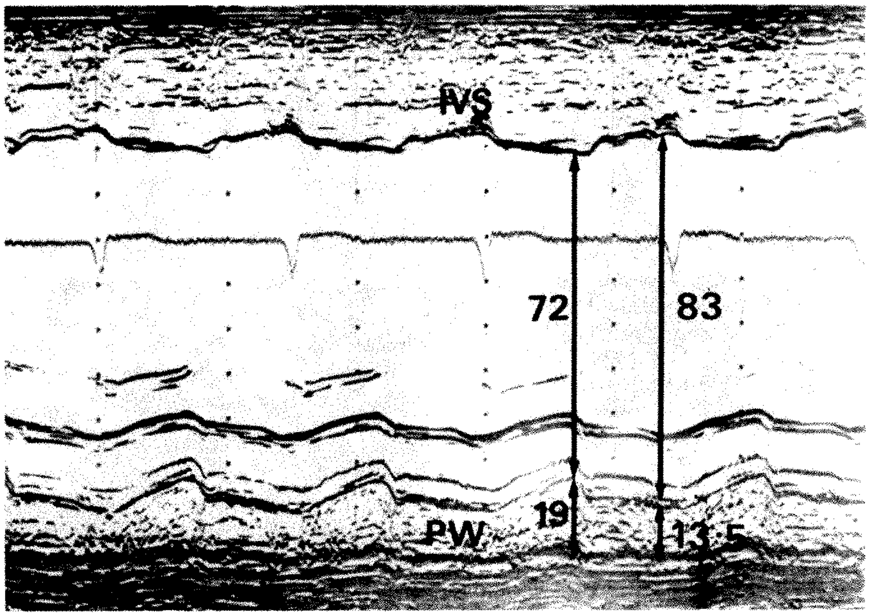

FIG. 2 *Patient with severe left ventricular failure (Case 29). Distinct difference between systolic and diastolic estimates of wall volume using both cube (26%) and ellipsoid (25%) formulae.*

overestimate end-systolic wall thickness, and hence wall volume, by angiocardiography (Hugenholtz *et al.*, 1969).

In conclusion, close agreement can be obtained between echocardiographic systolic and diastolic wall volume estimates. Having established this, comparison of wall volume estimates can be used to assess the reliability of measurements of ventricular dimensions and volumes in individual subjects. It is suggested that differences in excess of 10 per cent between systolic and diastolic left ventricular wall volume estimates point to lack of reliability of measurements of left ventricular volumes.

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# Pregnancy in patients after valve replacement

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*This report is based on information obtained from a questionnaire sent to major cardiac centres in the United Kingdom. This produced details of 39 pregnancies in 34 patients after valve replacement. The 39 pregnancies gave rise to 30 healthy babies. The small size of the series probably reflects both the increasing rarity of young women with rheumatic heart disease in this country and the cautious attitude of their cardiologists. This makes it likely that these women represented the best end of the spectrum of cardiac function after valve replacement.*

*Twenty-four pregnancies in 20 women who were not given anticoagulants produced 23 healthy babies and 1 spontaneous abortion. This group comprised 6 patients with free aortic homografts, 1 patient with a free fascia lata aortic valve, 2 with a Starr Edwards aortic valve, 7 with mounted mitral homografts, 1 with a fascia lata mitral valve, 1 with a Beall tricuspid prosthesis, 1 with a combined mitral homograft and Starr Edwards aortic prosthesis, and 1 with mitral and aortic frame-mounted fascia lata valves. There were no maternal deaths or thromboembolic complications in this group which included 5 patients who were in atrial fibrillation.*

*Fifteen pregnancies in 14 women who received anticoagulants gave rise to 7 healthy babies. The fetal losses were one stillbirth, one intrauterine death at 34 weeks, and 3 spontaneous abortions; one surviving child has hydrocephalus as a result of blood clot and there were 2 maternal deaths. This group included 13 patients with Starr Edwards valves, 11 mitral and 2 aortic. A patient with a Hammersmith mitral valve was the only one to have been treated with heparin and her valve thrombosed. One patient with a mounted mitral homograft had a cerebral embolus. Nine of these patients were in atrial fibrillation.*

*In 3 additional patients the valve replacement was carried out during pregnancy. Two of the patients survived operation. In one of these who was treated with warfarin the pregnancy gave rise to a congenitally malformed baby who died in the neonatal period. The baby born to the mother who did not receive anticoagulants has a hare-lip and talipes.*

*Women with artificial valves can tolerate the haemodynamic load of pregnancy well, but there is an increased fetal wastage in patients taking oral anticoagulants. This is probably largely attributable to fetal haemorrhage but there is also a risk of malformation caused by a teratogenic effect of warfarin. Experience gained in non-pregnant patients suggests that withholding anticoagulants in pregnant patients with prosthetic valves would usually be undesirable but warfarin should be avoided. The advantages of biological valves were apparent in this series.*

Although rheumatic heart disease has become rare among our indigenous youth, its prevalence in many parts of the world remains unchanged and the increasing frequency with which artificial valves are being used in the management of congenital and postinfective as well as rheumatic heart disease means that there is a growing population of women of child-bearing age who have had valve replacements. These women need to know the risks of pregnancy and the chances of having a healthy baby, but physicians and cardiologists cannot yet advise them honestly because of the limitations of individual experience.

A survey was undertaken to find out what the overall experience in the United Kingdom has been. Though there is a growing number of published reports they are mainly case reports, and we felt

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that many of the publications may have been inspired either by the success or by the failure of the pregnancy or pregnancies described and might not be true indicators of overall practice and experience.

## Patients

The questionnaire was sent to cardiologists in the United Kingdom and sought the following information.

(1) The patient's age, diagnosis, date of operation, and the interval between it and subsequent pregnancy; (2) the sites, models, and sizes of the artificial valves used: (3) the anticoagulant regimen adopted; (4) the use of other drugs including agents inhibiting platelet aggregation; (5) the course of the pregnancy with particular reference to the development of heart failure, valve dysfunction, embolism, or deep venous thrombosis; (6) the management of labour and the puerperium.

The section of the questionnaire which dealt with the baby inquired about (1) gestational age; (2) the general health at delivery; (3) the presence of congenital abnormalities, and (4) cerebral damage or jaundice.

The response to the questionnaire produced the details of 32 patients to which we added 5 of our own (Cases 5, 6, 7, 8, and 30—Table). The patients fell into 3 groups. The first group (Cases 1 to 30) consisted of patients who completed their pregnancies, 3 of whom have already been reported: Case 1 (Littler, 1970); Case 23 (Szekely and Snaith, 1969), and Case 30 (Bennett and Oakley, 1968). Nineteen patients were not given anticoagulants (Cases 1 to 19). Of these patients, 13 had homograft valves (6 aortic; 7 mitral), 1 an aortic fascia lata valve, 2 aortic Starr Edwards valves, 1 a Beall valve in the tricuspid position for Ebstein's disease, 1 a mitral homograft and a Starr Edwards aortic prosthesis, and 1 both mitral and aortic frame-mounted fascia lata valves. Eleven patients were treated with anticoagulants (Cases 20 to 30). These included 9 patients with Starr Edwards prostheses (7 mitral; 2 aortic), 1 with an Alvarez Hammersmith mitral valve, and 1 with a mounted mitral homograft who was started on anticoagulants after an embolus at 34 weeks. Warfarin was used in 5 patients, 5 received phenindione, and 1 (Case 20) received subcutaneous heparin in full anticoagulant doses.

In the second group, pregnancy was not completed (Cases 31 to 34). Two of these patients had Starr Edwards prostheses and received warfarin. The other had a fascia lata mitral valve and was not given anticoagulants.

The third group consisted of 3 patients who had a valve replacement performed during pregnancy (Cases 35 to 37). Two survived operation, 1 with a Starr Edwards mitral valve who received warfarin and 1 with a free aortic homograft to whom no anticoagulants were given.

The 11 patients in the first and second groups with aortic valve replacement alone were all in sinus rhythm. Seven had free aortic homografts or a fascia lata valve and did not receive anticoagulants. Only 2 of the 4 patients with a Starr aortic valve received anticoagulants. Of the 26 patients who had mitral, mitral plus aortic, or tricuspid valve replacement, 14 were in atrial fibrillation and 13 received anticoagulants. All the patients with Starr Edwards mitral valves received anticoagulants but only one of those with a mitral homograft did so; she was in sinus rhythm but had a cerebral embolus and anticoagulants were started at 34 weeks' gestation.

The intervals between cardiac operation and conception varied between 3 months and 5 years and the ages of the patients ranged from 18 to 38 years.

## Results

### Babies

Thirty-nine pregnancies in 34 women who conceived after valve replacement gave rise to 30 healthy babies. There were 3 spontaneous early abortions in women taking warfarin and 1 abortion occurring at 24 weeks in a patient who was not on anticoagulants (Cases 31 to 33). There were 2 late intrauterine deaths (Cases 26 and 27); both of these fetal deaths occurred in women who were receiving phenindione. One baby (Case 22) developed hydrocephalus secondary to a blood clot obstructing the third ventricle. As his birth had been by caesarian section at 38 weeks the cerebral bleed can almost certainly be attributed to the warfarin which his mother had received. This child has now had a shunt performed but is retarded and blind. The other two fetal deaths were the result of death of the mother.

Both of the women who survived valve replacement during pregnancy had malformed babies (Cases 35 and 37). The baby born to the patient who received warfarin (Case 35) had multiple congenital malformations and died in the neonatal period; this may have been chondrodysplasia punctata but not recognized as such. The hare-lip and talipes of the baby born to Case 37 must have been determined well before the time of cardiopulmonary bypass in mid-pregnancy, possibly during infective endocarditis.

The only fetal complications in the 20 women who did not receive anticoagulants were a spontaneous abortion at 24 weeks (plus the hare lip and

| *Case No.* | *Age* | *Site* | *Type* | *Anticoagulant Type* | *Stopped before term* | *Replaced with heparin* |
|---|---|---|---|---|---|---|
| 1 | 27 | Aortic | Homograft | None | | |
| 2 | 20 | Aortic | Homograft | None | | |
| 3 | 34 | Aortic | Homograft | None | | |
| 4 | 28 | Aortic | Homograft | None | | |
| 5 | 35 | Aortic | Homograft | None | | |
| 6 | 28 | Aortic | Homograft | None | | |
| 7 | 34 | Aortic | Fascia lata | None | | |
| 8 | 21 | Mitral | Mounted homograft | None | | |
| 9 | 18 | Mitral | Mounted homograft | None | | |
| 10 | 35 | Mitral | Mounted homograft | None | | |
| 11 | 26 | Mitral | Mounted homograft | None | | |
| 12 | 18 | Mitral | Mounted homograft | None | | |
| 13 | 26 | Mitral | Mounted homograft | None | | |
| 14 | 33 | Mitral | Mounted homograft | None | | |
| 15 | 34 | Tricuspid | Beall | None | | |
| 16 | 20 | Mitral aortic | Homograft SE | None | | |
| 17 | 33 | Mitral aortic | Frame-mounted fascia lata | None | | |
| 18 | 33 | Aortic | SE | None | | |
| 19 | 28 | Aortic | SE | None | | |
| 20 | 21 | Aortic | SE | Phenindione | Yes | No |
| 21 | 29 | Aortic | SE | Warfarin | Yes | Yes |
| 22 | 35 | Mitral | SE | Warfarin | Yes | Yes |
| 23 | 38 | Mitral | SE | Warfarin | Yes 24 hr before induction | No |
| 24 | 32 | Mitral | SE | Warfarin | Yes | Yes |
| 25 | 28 | Mitral | SE | Phenindione | Yes | Yes |
| 26 | 28 | Mitral | SE | Phenindione | No continued until delivery | No |
| 27 | 27 | Mitral | SE | Phenindione | Yes at 34/52 | Yes |
| 28 | 21 | Mitral | SE | Warfarin | Yes | Yes |
| 29 | 33 | Mitral | Mounted homograft | Warfarin from 34/52 | Yes | Yes |
| 30 | 36 | Mitral | Hammersmith Alvarez | Subcutaneous heparin | Continued | |
| 31 | 31 | Mitral | SE | Warfarin | | |
| 32 | 24 | Mitral | Fascia lata | None | | |
| 33 | ? | Mitral | SE | Warfarin | | Yes |
| 34 | 28 | Mitral | SE | Warfarin | | |
| 35 | 28 | Mitral | SE | Warfarin | Yes | Yes |
| 36 | | Mitral<br>tricuspid | SE<br>SE | None | | |
| 37 | 23 | Aortic | Homograft | None | | |

*Abbreviations:* SE=Starr Edwards; CCF=congestive cardiac failure; SBE=subacute bacterial endocarditis; PET = pre-eclamptic talipes in Case 37 already discussed). The other 19 patients enjoyed 23 successful pregnancies.

### Mothers

The maternal complications were few. The only patient who was treated with heparin throughout pregnancy rather than oral anticoagulants died. She was the only patient with a Hammersmith (Alvarez) prosthesis (Case 30); she received full anticoagulant doses of heparin subcutaneously throughout pregnancy and though she had enjoyed 3 years of good health since her valve replacement the valve became encapsulated by thrombus and fibrin when she was 33 weeks' pregnant (Bennett and Oakley, 1968). In the second group, one patient who was on warfarin died at 32 weeks after rupture of a common iliac aneurysm; this was thought to be a complication of previous infective endocarditis (Case 34). There was one maternal death in the third group and this resulted from postoperative complications following double valve replacement during the second trimester of pregnancy (Case 36). None of these major maternal complications can be attributed to the use of anticoagulants, though warfarin may have contributed to the fatal bleeding from the common iliac artery. There were 3 other minor complications attributable to anticoagulants: Cases 20 and 21 had postpartum haemorrhages and Case 22 developed a small haematoma of her abdominal wall after caesarian section.

Apart from Case 30 there was only one thromboembolic complication in either group: Case 29 was in sinus rhythm with a mounted mitral homograft but had a cerebral embolus at 34 weeks; she was started on anticoagulants and the outcome was good.

The patients seemed to deal easily with the haemodynamic stresses of pregnancy and congestive failure was noted in only 2 patients. In neither was it a worry and both recovered well after a period of bed rest and diuretics. One was 35 years old with a mounted mitral valve prosthesis and atrial fibrillation (Case 10) and the other was a 33-year-old in sinus rhythm who was one of the only two patients in whom both mitral and aortic valves had been replaced, one of which was subsequently found to be leaking slightly (Case 17).

## Discussion

An increase in cardiac output of up to 50 per cent above the non-pregnant level is achieved in pregnancy by an increase in stroke volume without an increase in rate. Provided the left atrium can empty freely even the disabled heart can adapt satisfactorily to pregnancy by an increase in rate to

| *Course of pregnancy* | *Fetal complications* |
|---|---|
| Mild PET, vaginal delivery at term | Normal baby |
| Uncomplicated delivery, vaginal delivery at term | Normal baby |
| Normal vaginal delivery | Normal baby |
| Normal vaginal delivery | Normal baby |
| Uncomplicated | Normal baby |
| Caesarian section 39/52 | Normal baby |
| 2 normal pregnancies | 2 healthy babies |
| Forceps delivery 39/52, uncomplicated | Normal baby |
| Uncomplicated, vaginal delivery at term | Normal baby |
| Mild CCF, vaginal delivery by forceps at term | Normal baby |
| Normal vaginal delivery | Normal baby |
| Normal vaginal delivery | Normal baby |
| 2 normal pregnancies | 2 healthy babies |
| Uncomplicated | Healthy baby |
| 2 pregnancies, both uncomplicated | 2 normal babies |
| 2 pregnancies | 2 healthy babies |
| CCF at 33 weeks, back to grade II by delivery | Healthy baby |
| Uncomplicated | Normal baby |
| Uncomplicated | Normal baby |
| Uncomplicated, postpartum haemorrhage | Normal baby |
| Uncomplicated, postpartum haemorrhage | Normal baby |
| Uncomplicated, small haematoma of abdominal wall after caesarian section 38/52 | Hydrocephalus with organized clot obstructing 3rd ventricle, shunt performed, retarded and blind |
| Uncomplicated, normal vaginal delivery | Healthy baby, 2 mg vit. $K_1$ given at birth |
| Uncomplicated, normal vaginal delivery | Normal baby |
| Uncomplicated, caesarian section 37/52 | Normal baby |
| Started on diuretics at 20/52, reason not specified | Macerated stillborn |
| Induced at 34/52 because of intrauterine death | Necropsy: no cause for death |
| Uncomplicated low forceps | Normal baby |
| Cerebral embolus 34/52 | Normal baby |
| Caesarian hysterectomy 33/52, thrombosed prosthetic valve, died 6 days postpartum | Neonatal death at 9 hours |
| 2 pregnancies, spontaneous abortions at 8 and 11 weeks | |
| Spontaneous abortion at 24/52 | |
| Missed abortion at 15 weeks, warfarin changed to heparin before D and C | |
| Patient died at 32/52 of ruptured common iliac aneurysm, ?complication of previous SBE | |
| Valve replaced during pregnancy at 20/52, caesarian section 38/52 | Neonatal death, congenital malformations |
| Valves replaced during pregnancy, patient died of post-op complications | |
| Developed SBE, valve replaced during pregnancy, normal vaginal delivery | Hare-lip and talipes |

toxaemia; D and C = dilatation and curettage compensate for any inability to increase stroke volume.

While many patients who have had aortic valve replacement for congenital or postinfective aortic valve disease have nearly normal cardiac function most patients with rheumatic mitral or multivalvular disease still have considerably impaired cardiac performance after operation and many are in atrial fibrillation. Despite this, it has become apparent that many patients can easily cope with the demands of pregnancy after valve replacement (Ueland, Tatum, and Metcalfe, 1966; Barnard and Heydenrych, 1969; Radnich and Jacobs, 1970; Jenkins and Braimbridge, 1971; Ibarra-Pérez and Del Bosque-Ruiz, 1972). Only 1 maternal death occurred among 95 completed pregnancies reported up to the end of 1975 (Mahairas and Weingold, 1963; Palacios-Macedo, Díaz-Devis, and Escudero, 1969; Laros, Hage, and Hayashi, 1970; Macdonald, 1970; Buxbaum *et al.,* 1971; Jenkins and Braimbridge, 1971; Hirsh, Cade, and Gallus, 1972; Casanegra *et al.,* 1975; Chew and Ratnam, 1975). This was our Case 30, previously reported (Bennett and Oakley, 1968) and her death was caused by thrombosis of her mitral valve and not by any haemodynamic inadequacy existing before this complication. Even triple valve replacement can allow safe and successful pregnancy, yet accompanying their replies to the questionnaire a number of cardiologists spontaneously referred to their 'vigorous sterilization policy' or volunteered that they 'would never permit a patient with an artificial valve to undertake pregnancy'. Few of our patients became pregnant against the advice of their cardiologists and their cautious attitude indicates the selected nature of our material. We see a predominance of single valve replacements, of biological valves, and of sinus rhythm in this series.

The general care of these patients during pregnancy does not differ in principle from that of pregnant patients with valvular heart disease who have not had valve replacements. Current practice has been well reviewed by Szekely, Turner, and Snaith (1973) and by Conradsson and Werkö (1974). There are, however, some aspects of management which take on special importance and warrant further discussion.

In contrast to the good experience of the mothers the fetal mortality is high. That this is not a necessary consequence of the maternal disease is shown by the experience of Szekely and his colleagues (1973) in Newcastle who reported a perinatal mortality of under 5 per cent in over 200 patients with rheumatic heart disease between 1961 and 1969 (with no maternal mortality). This high fetal mortality is intimately connected with the use of oral anticoagulants. All 23 completed pregnancies in women who were not receiving anticoagulants produced healthy babies in this series. There was no fetal or neonatal mortality or morbidity and the only congenital malformations were in Cases 35 and 37 who had a valve replaced during pregnancy. Buxbaum *et al.* (1971) reported a similar experience in 6 patients.

When considering whether or not to continue oral anticoagulants the risk to the fetus if they are used has to be weighed against the risk of thromboembolism in the mother if they are stopped. Experience in non-pregnant patients indicates that anticoagulants are effective in reducing the incidence of thromboembolic complications after valve replacement (Akbarian *et al.,* 1968). During pregnancy the concentration of most coagulation factors in the blood is increased and fibrinolysis is decreased (Hedstrand and Cullhed, 1968), but despite this there is little evidence of increased risk of pulmonary thromboembolism during normal pregnancy (Villasanta, 1965; Bonner, 1975) probably because of the increased cardiac output. There is a real risk of embolism in patients with prosthetic valves whose anticoagulants are stopped or interrupted during pregnancy (Akbarian *et al.,* 1968; Jenkins and Braimbridge, 1971) and in the cases reviewed by Buxbaum *et al.* (1971) there were 4 embolic episodes in 8 patients compared with only 3 in 29 pregnancies covered with anticoagulants throughout. However, Sowinsky, Zdebski, and Haduch-Kowalczyk (1972), reviewing 15 cases who had not received anticoagulants in pregnancy, found only 1 who had suffered a thromboembolic episode. Experience with the newer cloth-covered Starr Edwards valves shows that there has been a decrease in the incidence of embolic episodes (Isom *et al.,* 1972). The trend, which applies particularly to aortic prostheses, becomes more obvious the longer the valve is *in situ* and is attributed to endothelialization of the supporting structures of the prosthesis. Unfortunately, the protection from thromboembolic risk conferred by any of the newer artificial valves is not absolute. There is a higher incidence of embolism in patients with mitral than with aortic prostheses because these patients more frequently have atrial fibrillation and large atrial cavities and appendages. Anticoagulants are mandatory in such patients but are still recommended in patients with aortic prostheses. Anticoagulants are usually not needed after tissue valve replacement. Thromboembolism is virtually unknown after free aortic homograft insertion and seems to be rare after replacement of the mitral valve with stented aortic homografts despite the frequency of atrial fibrillation. The only embolic episode in the series was in such a patient (Case 29) despite sinus rhythm when seen. The advantages of a biological valve in a young woman who may wish to have a family are apparent even though these valves may show less long-term durability than the artificial valves.

The formation of thrombus in relation to prostheses has been shown to be the result of the build-up of adherent platelet aggregates and the deposition of fibrin (Mustard *et al.*, 1966). This has led to the use of 'antiplatelet aggregating' agents, of which dipyridamole (Sullivan, Harken, and Gorlin, 1971) and aspirin (Stuart *et al.*, 1974) have proved to be effective when combined with warfarin, but whether they will be safe in pregnancy or effective when used on their own has yet to be shown. There is one case report (Ben Ismail *et al.*, 1975) of a woman with 3 prosthetic valves in whom warfarin was replaced by 1·5 g aspirin and 225 mg dipyridamole daily at 2 months' gestation and who continued to term with a successful outcome.

Oral anticoagulants of the coumarin and indanedione groups cross the placental barrier and reach the fetus whose state of anticoagulation is likely to be different from that of the mother as well as unmeasurable. Because of immature fetal liver enzyme systems the baby is likely to grow in a continuing state of anticoagulant overdose if the mother's state of anticoagulation is within the therapeutic range. It is probably more dangerous to give oral anticoagulants early in pregnancy because the fetus is then at its most vulnerable both from bleeding and from the teratogenic effects of these drugs (*vide infra*). A small haemorrhage can at this time produce severe damage because of the close proximity of the developing structures.

The evidence that these are real hazards comes from Mahairas and Weingold (1963) and the review by Villasanta (1965) later supported by Fillmore and McDevitt (1970). Villasanta related the experience of 93 women who were treated with oral anticoagulants during their pregnancies, resulting in 14 stillbirths, 3 neonatal deaths, and 2 congenital malformations. He concluded that oral anticoagulant drugs should not be prescribed during pregnancy. Villasanta's experience that 16 per cent of the babies suffered brain damage attributable to haemorrhage *in utero* was particularly alarming as most of the mothers studied by him had received anticoagulants for venous thrombosis and so had only been treated for a few weeks rather than throughout pregnancy. The risk of intrauterine death was reported also by Palacios-Macedo *et al.* (1969) who described 3 stillbirths occurring in 6 patients with prosthetic valves, in 1 of whom multiple haemorrhages were found at necropsy and in another the fetus had probably died at a time when there was excessive anticoagulant effect in the mother. Poor anticoagulant control is likely to compound the risks. The case reported by Kenmure (1968) was an example of the kind of patient who fortunately does not appear in our series; in her 40s and diabetic with an accidental pregnancy, she had a mitral Starr valve and was in atrial fibrillation, with a history of postoperative cerebral embolism: the baby was stillborn at 33 weeks.

Mahairas and Weingold showed a connexion between depression of prothrombin activity and perinatal haemorrhage if oral anticoagulants were continued during delivery. Experimental evidence that the trauma of vaginal delivery is also a major risk factor in the production of perinatal cerebral haemorrhage is available from the work of Hirsh, Cade, and O'Sullivan (1970) who showed that widespread haemorrhage occurred in the fetuses of rabbits who were given warfarin until term; all were stillborn. In those cases reviewed by Villasanta (1965) who were receiving oral anticoagulants up to term there were 5 cases of perinatal haemorrhage, 4 of which proved fatal. Hirsh's group showed that no perinatal haemorrhage occurred if fetal clotting factors were allowed to return to normal by stopping warfarin a few days before delivery, or even in the presence of depressed fetal coagulation factors if delivery were by caesarian section. The usual practice now is for patients to have their oral anticoagulant changed to heparin, which does not cross the placenta, at least two weeks before term. This will not always be possible if labour starts prematurely, and vitamin $K_1$ or fresh frozen plasma given to the mother may not have time to correct the depressed fetal clotting state before delivery. Premature labour may be an indication for caesarian section when the mother is on oral anticoagulant treatment.

Maternal bleeding requiring transfusion during labour is rare. There are 3 cases reported by Buxbaum *et al.* (1971) in association with the use of heparin. Haematomas in episiotomy sites or in caesarian scars (Case 22) do occur and show the need for scrupulous haemostasis (Hirsh *et al.*, 1970, 1972).

Anticoagulants need to be used, so what is the best regimen to adopt? Heparin throughout pregnancy would be expected to remove the fetal hazards but is not always a practical possibility. The use of self-administered subcutaneous injections of heparin have recently been shown (Bonner, 1975) to produce effective blood levels. Though its successful use in pregnancy has been reported (Otterson, McGranahan, and Freeman, 1968) and subcutaneous heparin has the advantage of allowing therapy to be controlled on an outpatient basis, its effectiveness during pregnancy is still unknown. Even though it was used in full anticoagulant dosage in Case 30 the results were disastrous. The lack of standardization of available heparin preparations is another problem (Jaques, 1975). A compromise would be to use heparin in the first trimester, then to substitute oral anticoagulants until 2 to 3 weeks before term, when heparin is reintroduced. Hirsh *et al.* (1970) used this regimen in 15 pregnancies and had no fetal or neonatal complications. The obvious difficulty about this counsel of perfection would be the accurate prediction of the future conception in order to change the regimen in time.

Oral anticoagulant treatment is re-established after delivery. The presence of anticoagulant in the breast milk is not a significant problem compared with the higher concentration to which the baby had been exposed *in utero.* All babies should routinely be given vitamin $K_1$ at birth.

Although the high fetal wastage can be attributed largely to the oral anticoagulant treatment it is not wholly consequent upon bleeding. A teratogenic effect of anticoagulants first suggested by Villasanta is now well substantiated. Stippled epiphyses have been reported in 7 babies after warfarin (Fourie and Hay, 1975; Pettifor and Benson, 1975; Becker *et al.*, 1975; Shaul, Emery, and Hall, 1975). This condition, also known as chondrodysplasia punctata or the Conradi-Hunermann syndrome, causes saddle nose deformity, nasal hypoplasia, frontal bossing, and short stature. Inconstant features include optic atrophy, cataracts, mental retardation, and flexion contractures. There was no definite example of this condition in our series except, possibly, for the baby of Case 35. It appears three times in the reports of pregnancy after valve replacement; DiSaia's (1966) patient whose baby had nasal hypoplasia and optic atrophy, Kerber, Warr, and Richardson's (1969) patient whose baby had nasal hypoplasia, and Tejani's (1973) patient whose baby had nasal hypoplasia and multiple neurological abnormalities. All 3 of these patients had received warfarin throughout the pregnancy until the 31st, 35th, or 36th week when heparin was substituted. According to Fourie and Hay (1975), chondrodysplasia punctata is a rare embryopathy whose incidence has been estimated at 1 in 500 000 births and which otherwise is hereditary, occurring in a severe autosomal recessive and a milder autosomal dominant form. It seems unlikely, therefore, that the association with warfarin administration is a chance one. Perhaps an indanedione rather than a coumarin drug should be chosen for anticoagulant management in young women, but this raises the problem of renal and hepatic failure after phenindione. Though this complication rarely occurs without preceding skin eruption many would regard the teratogenic risk of coumarin to the baby as preferable to the probably greater risk of phenindione to the mother.

The subject of family planning should be approached early in patients who are likely to require a valve replacement during their childbearing years. They should be advised when possible to have their children before valve replacement unless they have lone aortic valve disease and homograft aortic valve replacement is available for them. Mounted mitral homograft valves or other forms of tissue mitral valves are less generally available and less favoured but all except one of the patients with such valves in our series did well without anticoagulant treatment. Mitral regurgitation and multivalvar disease is less dangerous than pure mitral stenosis in pregnancy because of a lesser risk of pulmonary oedema. While mitral valvotomy can be carried out safely in pregnancy and should not be delayed when the valve is suitable, vigorous medical management of a woman who will need valve replacement is still worth while in order to take her through pregnancy before cardiac surgery is undertaken. While open heart surgery can be carried out successfully during pregnancy, in most institutions it is not yet as safe for the baby as a closed procedure so that deferral of open heart surgery and choice of closed rather than open mitral valvotomy seems to be wise at the present time. In the 3 cases we report who underwent valve replacement during pregnancy (Cases 35 to 37), there was one maternal and fetal death resulting from postoperative complications and the 2 babies who survived birth had congenital malformations. Zitnik *et al.* (1969) reported 3 patients who underwent valve replacement during pregnancy, all of whom survived. Two of these had normal babies; the other who was operated on at 19 weeks had a spontaneous abortion three days after operation. These were included in a series of 20 patients who had open heart surgery during pregnancy. Among these there was one maternal death in a patient with an atrial septal defect, and a high fetal mortality of 33 per cent. Zitnik recommended that operation should be performed after the 28th week when organogenesis is complete and suggested short bypass times with high flow to provide maximal placental perfusion.

## Conclusion

A review of previously reported cases in addition to our own series indicates that most patients with artificial valves can safely undertake pregnancy. If the patient who is taking an anticoagulant understands that there is an increased risk to the baby but is still keen, then future pregnancy need nto be discouraged. Patients with tissue valves who do not require an anticoagulant after valve replacement can undertake pregnancy with a normal expectation of achieving a healthy baby. For this reason biological valves maintain an advantage over other types of prostheses in young women. For those patients who need to be on an oral anticoagulant there is an increased risk of abortion, stillbirth, perinatal mortality, and morbidity and, in addition, a risk of fetal malformation caused by warfarin. An alternative anticoagulant should be considered when young women are started on anticoagulants after valve replacement.

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# Malfunction of Björk-Shiley valve prosthesis in tricuspid position

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*Eight months after triple valve replacement with Björk-Shiley tilting disc valves a patient developed symptoms and signs suggesting malfunction of the prosthesis in the tricuspid position. This was confirmed by echocardiography and angiocardiography, and at operation the disc of the prosthesis was found to be stuck half-open by fibrin and clot. A further 11 patients with the same type of prosthesis in the tricuspid position were then studied by phonocardiography and echocardiography. In one of these the prosthesis was found to be stuck and this was confirmed by angiocardiography and surgery. These 2 cases are reported in detail and the findings in the other 10 are discussed. The implications of this high incidence of malfunction of the Björk-Shiley prosthesis in the tricuspid position are considered. Echocardiography appears to be essential in the follow-up of such patients.*

Obstruction of ball valve prostheses in the tricuspid position is well recognized (Samaan and Murali, 1970; Vander Veer *et al.*, 1971; Bache *et al.*, 1972; Suwansirikul *et al.*, 1974; Assad-Morell *et al.*, 1974). Assad-Morell *et al.* (1974) emphasized the value of phonocardiography and echocardiography in the diagnosis of this complication. Echocardiography has been used by a number of workers in the analysis of normal prosthetic valve function (Gimenez *et al.*, 1965; Winters, Gimenez, and Soloff, 1967; Johnson, Paton, and Holmes, 1970; Johnson, Holmes, and Paton, 1973; Douglas and Williams, 1974), and there have been reports of its use in the diagnosis of malfunction of prosthetic valves (Pfeifer *et al.*, 1972; Belenkie *et al.*, 1973; Oliva *et al.*, 1973; Miller, Gibson, and Stephens, 1973). We have, however, found no previous reports of malfunction of the Björk-Shiley tilting disc valve in the tricuspid position. The present study followed the discovery of a stuck prosthesis of this type in the tricuspid position in one patient (Case 1), and led to the discovery of another (Case 4).

## Subjects and methods

After the diagnosis and successful treatment of Case 1 a further 11 patients with a Björk-Shiley disc valve prosthesis in the tricuspid position were studied. They were numbered (Table) in the order of their study. All patients were on anticoagulant therapy. Clinical examination and penetrated posteroanterior and lateral chest *x*-ray films were examined in every case. From these *x*-ray films the alignment of the disc of the prosthesis was determined and documented according to the direction of the small segment of the disc. Phonocardiograms and echocardiograms were recorded on a Cambridge strip-chart recorder. Echocardiography was performed using a Smith Klein Ekoline 20, and a 2·25 MHz transducer focused at 5 cm. The transducer was placed at the left sternal border in the fourth or fifth intercostal space and the patient was positioned so as to produce the clearest recording of the valve disc. The optimal position was usually supine or lying on the left side at an angle of about 45°. The excursion of the opening movement of the disc of the prosthesis in the tricuspid position was measured as shown in Fig. 1A.

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## Results

The details are shown in the Table. In Cases 1 and 4 no movement of the disc of the prosthesis was recorded, but in all the others opening and closure were shown.

### Case 1

A 66-year-old man had severe triple valve disease

TABLE *Details of patients with a Björk-Shiley valve prosthesis*

| *Case No.* | *Age (y)* | *Sex* | *Valves replaced* | *Tricuspid size (mm)* | *Months from operation to study* | *Orientation of disc (small segment)* | *Disc excursion (cm)* | *No. of AV valve closing sounds* | *No. of AV valve opening sounds* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 66 | M | M, T, A | 31 | 8 | Inferior | Nil | 1 | 1 |
| 2 | 35 | F | M, T, A | 29 | 7 | Posterior | 1·3 | 2 | 1 |
| 3 | 61 | M | M, T, A | 31 | 12 | Inferior | 1·3 | 1 | 2 |
| 4 | 48 | F | M, T, A | 31 | 15 | Superior | Nil | 1 | 1 |
| 5 | 50 | F | M, T, A | 31 | 22 | Superior | 1·0 | 2 | 1 |
| 6 | 49 | F | M, T, A | 31 | 12 | Superior | 1·6 | 2 | 2 |
| 7 | 45 | F | M, T | 31 | 7 | Superior | 1·35 | 2 | 1 |
| 8 | 69 | F | M, T | 29 | 10 | Superior | 0·85 | 2 | 1 |
| 9 | 37 | F | M, T, A | 31 | 22 | Superior | 0·9 | 2 | 2 |
| 10 | 48 | F | M, T, A | 31 | 14 | Posterior | 1·0 | 2 | 2 |
| 11 | 69 | F | M, T, A | 31 | 1 | Superior | 1·1 | 2 | 1 |
| 12 | 52 | F | M, T, A | 31 | 24 | Posterior | 1·0 | 2 | 2 |

M, mitral; T, tricuspid; A, aortic.

*Note:* All prosthetic valves were Björk-Shiley prostheses, except for Case 10 in whom the mitral and aortic prostheses were Starr-Edwards ball valve prostheses.

and a history of rheumatic fever. Cardiac catheterization had confirmed severe mitral stenosis and moderate mitral regurgitation, moderate aortic stenosis and mild aortic regurgitation, and moderate tricuspid regurgitation, with severe pulmonary hypertension. A triple valve replacement was performed using Björk-Shiley prostheses. He subsequently did well until eight months after the operation when he began to feel weak and tired, with ankle swelling and moderate exertional dyspnoea. He had required admission to another hospital for restabilization of his anticoagulants about a month earlier because he had had too high a dosage. Otherwise his anticoagulation had been satisfactory. On examination he had mild ankle oedema and 3 cm hepatomegaly, and the jugular

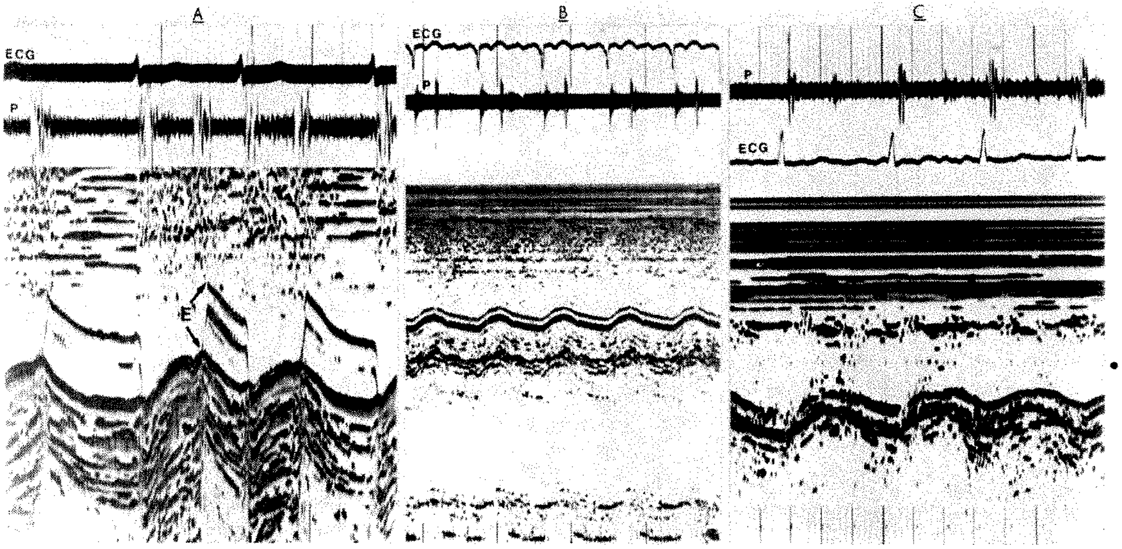

FIG. 1 *Echocardiograms of tricuspid valve prostheses. (A) Functioning prosthesis in Case 3; disc excursion (E) was measured between the two black arrows. (B) Stuck prosthesis in Case 1. (C) Stuck prosthesis in Case 4. P = phonocardiogram.*

venous pressure was raised to about 10 cm above the sternal angle. He was in controlled atrial fibrillation. On auscultation there was a grade 3/4 delayed diastolic murmur, heard maximally at the lower left sternal edge, and increasing in intensity with inspiration. There was also a soft pansystolic murmur at the left sternal edge and a soft aortic systolic murmur. The prosthetic valve sounds were considered clinically to be normal. The diagnosis was thought to be malfunction of the tricuspid valve prosthesis, with resulting stenosis and regurgitation.

Phonocardiography confirmed the clinical description of the murmurs and showed only single atrioventricular (AV) valve opening and closing sounds. Echocardiography of the tricuspid valve prosthesis showed two parallel lines with no evidence of an opening movement (Fig. 1B). The mitral and aortic valve prostheses were considered to be functioning normally. Right and left heart catheterization was performed. There was a high right atrial pressure with a mean of 14 mmHg and a *v* wave of 22 mmHg. An end-diastolic tricuspid gradient of 12 mmHg was recorded on withdrawal across the prosthesis. Angiocardiography with right atrial injection showed that the disc of the prosthesis was immobile in the half-open position. Mitral and aortic prosthetic valve function was normal. The diagnosis of thrombotic obstruction of the tricuspid valve prosthesis was made. At operation there was a fibrinous covering of the valve struts causing the disc to be held in the half-open position and to be completely immobile (Fig. 2). The valve was excised and a Starr-Edwards ball valve prosthesis was inserted. The patient has remained well since the operation and is now on dipyridamole as well as warfarin.

### Case 4

A 48-year-old woman had triple valve disease which was thought to be rheumatic in origin and had been complicated by infective endocarditis five years previously. Cardiac catheterization confirmed the presence of severe mitral regurgitation and stenosis, moderate aortic regurgitation with mild stenosis, and moderate tricuspid regurgitation and stenosis. A triple valve replacement was performed using Björk-Shiley valve prostheses. Subsequently she did well and was asymptomatic until one year after the operation when at a routine follow-up assessment she complained of a 'bloated' feeling and of having gained 12 kg in weight. Her exercise tolerance was however unchanged. The jugular venous pressure was noted to be moderately raised but the prosthetic valves were thought to be working normally. Four months later she was seen as part of the present study, initiated after the discovery of Case 1. She had by now developed ankle swelling in addition to her previous symptoms but exercise tolerance was still normal.

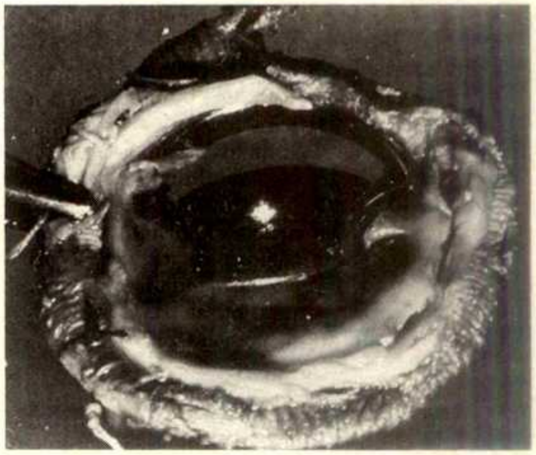

FIG. 2 *Excised prosthesis from Case 1 showing the disc of the valve stuck in the half-open position by fibrin covering the struts of the prosthesis. The excised prosthesis from Case 4 had a similar appearance though the fibrin covering the struts was less extensive. There was no evidence of infection on either valve prosthesis.*

Clinical examination revealed a high jugular venous pressure with a *v* wave 12 cm above the sternal angle. There was bilateral ankle oedema and 4 cm hepatomegaly. On auscultation there was a grade 1 delayed diastolic murmur at the lower left sternal edge, increased in intensity by inspiration. The prosthetic valve sounds were considered to be clinically unremarkable and an aortic ejection murmur was present. The murmurs were confirmed by phonocardiography but no tricuspid valve sounds could be identified, there being only single AV valve opening and closing sounds. Echocardiography of the tricuspid valve prosthesis showed two parallel lines with no opening movement (Fig. 1C), an appearance very similar to that found in Case 1 (Fig. 1B). This was thought to indicate that the disc of the prosthesis was stuck. Right atrial angiocardiography showed a filling defect on the ventricular aspect of the prosthesis. The disc could be identified and was seen to be stuck in the half-open position. Fluoroscopy, with the valve in profile, confirmed that the disc could be visualized and that it was stuck half-open and virtually immobile. At operation the valve was found to be obstructed by clot of varying ages and fibrin, with the disc stuck half-open. It was replaced by a Hancock mounted xenograft valve. The patient made a good recovery and is now asymptomatic, two months after the second operation.

### Other cases

All the other 10 patients studied (Cases 2, 3, and 5 to 12) were either asymptomatic or had minimal effort dyspnoea apart from Case 6 who had mild effort dyspnoea and Case 12 who had severe effort dyspnoea. The jugular venous pressure was mildly raised in Case 6, considerably raised in Case 12 and was normal in the other patients. Cases 6, 11, and 12 had soft delayed diastolic murmurs, and these were thought to arise from the tricuspid valve prostheses. However, in all cases the echocardiogram of the tricuspid valve prosthesis showed clear opening and closing movements (Fig. 1A).

The phonocardiogram was examined for two sounds of AV valve opening and two sounds of AV valve closure. Five patients had two AV valve opening sounds and 9 had two AV valve closing sounds (Table). None of these 10 patients had both a single AV valve opening sound and a single AV valve closing sound. It was concluded that the disc of the tricuspid valve prosthesis was not stuck in any of these 10 patients. The maximum disc excursion of the tricuspid valve prostheses which were not stuck varied from 1·6 cm to 0·85 cm (mean 1·1 cm). The excursion did not seem to be related to the orientation of the disc or to the size of the prosthesis.

## Discussion

Twelve patients with a Björk-Shiley prosthesis in the tricuspid position are presented. In 2 of them the disc of the prosthesis was stuck in the half-open position. Both of these patients had a pronounced rise in the jugular venous pressure and a delayed diastolic murmur, though in one of them (Case 4) the murmur was soft and could easily have been overlooked if attention was not paid specifically to this point. These physical signs, therefore, suggest the diagnosis of a stuck tricuspid valve prosthesis but they may be found when the disc of the prosthesis is shown to be mobile on the echocardiogram, as in Cases 6, 11, and 12. It is not possible to say from this study whether or not there were minor degrees of tricuspid prosthetic valve malfunction in these patients.

The phonocardiogram was found to be of limited use in making the diagnosis of a stuck tricuspid valve prosthesis. These patients all had mitral as well as tricuspid prostheses and all but two had aortic prostheses as well. This makes analysis of heart sounds very difficult even with the aid of simultaneous echocardiography. Some patients with both functioning mitral and tricuspid valve prostheses had single AV valve opening or closing sounds. Only the two patients with stuck tricuspid prosthetic valves, however, had both a single opening sound and a single closing sound.

Although angiocardiography was performed to confirm the diagnosis in the two cases with stuck prostheses reported here, the appearance on the echocardiogram of two parallel lines with no disc movement appears to be diagnostic. We believe that the two lines arise from the valve ring and the stationary disc. In a prosthesis that is opening the disc is seen to move anteriorly in diastole. The cause of an apparent double disc echo in some cases (Fig. 1A) is uncertain. Douglas and Williams (1974) emphasized the importance of the alignment of the disc and transducer in the echocardiographic assessment of Björk-Shiley prosthetic valves but this does not seem to be important in the detection of an immobilized disc in a prosthesis of this type in the tricuspid position.

Fluoroscopy showed the stuck disc in Case 4. In a normally functioning Björk-Shiley prosthesis the disc is not visible on fluoroscopy but it appears that when it is stationary and can be viewed in profile the disc can be visualized. Recently a radio-opaque ring has been incorporated in the discs of Björk-Shiley prostheses and the diagnosis of a stuck prosthesis of this modern type should be obvious on simple fluoroscopy. It seems reasonable to suggest that only this type of Björk-Shiley prosthesis should, in future, be used.

The incidence of malfunction of 2 out of 12 cases in our study may be an underestimate of the overall incidence as a further 5 patients who have had this type of prosthesis in the tricuspid position in this centre could not be included in this study. Three of these patients are overseas and 2 have died. Necropsy information on the state of the tricuspid valve prosthesis in these 2 patients is unfortunately not available.

It is of interest that in Case 4 there was thrombus of different ages on the valve at the time of operation and that some was recent. It appears from this observation that the lesion is progressive once it has started. It may be inferred that if anticoagulation is allowed to become inadequate even for a short time the process may start by which eventually prosthetic valve function may be destroyed by immobilization of the disc.

In reporting a case of late thrombosis of a ball valve prosthesis in the tricuspid position, Suwansirikul *et al.* (1974) thought that this was the result of entrapment of the cage of the valve in the wall of the right ventricle. This mechanism cannot be implicated with the low profile Björk-Shiley valve prosthesis. Other factors must, therefore, be of importance in the apparent predisposition of tricuspid valve prostheses to thrombotic obstruction, such as the dynamics of flow in the right side of the heart as compared with the left.

## Conclusion

The Björk-Shiley valve prosthesis is not the ideal valve for the tricuspid position. In cases with this type of prosthesis in the tricuspid position regular follow-up should be undertaken, paying particular attention to the jugular venous pressure and the presence of a diastolic murmur. Echocardiography should be performed frequently and it may be that serial studies would enable lesser degrees of tricuspid valve prosthetic malfunction to be detected before complete sticking of the disc. We suggest that in future if Björk-Shiley prostheses are used, only those with a radio-opaque ring incorporated in the disc should be employed.

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# Intraoperative left ventricular perforation with false aneurysm formation

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*Two cases of perforation of the left ventricle during mitral valve replacement are described. In the first case there was perforation at the site of papillary muscle excision and this was recognized and successfully treated. However, a true ventricular aneurysm developed at the repair site. One month after operation rupture of the left ventricle occurred at a second and separate site on the posterior aspect of the atrioventricular ring. This resulted in a false aneurysm which produced a pansystolic murmur mimicking mitral regurgitation. Both the true and the false aneurysm were successfully repaired. In the second case perforation occurred on the posterior aspect of the atrioventricular ring and was successfully repaired. However, a false ventricular aneurysm developed and ruptured into the left atrium producing severe, but silent, mitral regurgitation. This was recognized and successfully repaired. The implications of these cases are discussed.*

Left ventricular perforation during mitral valve replacement is an uncommon event but when it occurs it is often lethal (Roberts and Morrow, 1967; MacVaugh, Joyner, and Johnson, 1971). It can occur at the posterior aspect of the atrioventricular groove or at that portion of the left ventricle which overlies the papillary muscles (Treasure, Rainer, and Sadler, 1974). False ventricular aneurysm formation is a rare complication of myocardial infarction (Gueron *et al.*, 1974), non-penetrating chest wall trauma (O'Reilly, Kazenelson, and Spellberg, 1970), left ventricular incision (Kerr, Wilcken, and Steiner, 1961; Wychulis *et al.*, 1971), and of a left ventricular diverticulum (Layton and Hately, 1975). Spellberg and O'Reilly (1972) reported 2 cases of false ventricular aneurysm that followed mitral valve replacement and were thought to be related to the mobilization of the left ventricle from dense pericardial adhesions. We report 2 cases in which ventricular perforation occurred during mitral valve replacement and was later complicated by false aneurysm formation. This is out of a total of 343 patients undergoing mitral valve replacement at this centre over the past 3½ years.

## Case reports

### Case 1

A 60-year-old woman presented with a mildly regurgitant, severely stenosed, and heavily calcified mitral valve. There was minimal aortic regurgitation and the left ventricular cavity was of normal size.

At operation (22 November 1974) the calcification was found not to involve the mitral annulus and there was only moderate disease of the subvalvar mechanism. A 27 mm Björk-Shiley prosthesis was inserted using multiple interrupted sutures. While attempting to come off bypass the pericardium was found to be filling with blood. Bypass was restarted and a tear was found in the posterior left ventricular wall where the papillary muscle had been removed. The left anterior descending artery and branches of the circumflex coronary artery on either side of the defect were intact. The tear was closed using 'teflon' reinforced mattress sutures and a second layer of continuous sutures. The closure appeared to be effective and bypass was terminated successfully. A haematoma was, however, noted in the atrioventricular groove.

Recovery was uneventful and no murmurs were detected. The electrocardiogram, previously normal apart from mitral P waves, now showed right axis deviation and a broad prominent R wave in lead V1 (Fig. 1A and B). This was thought to indicate a strictly posterior myocardial infarction. Progress, however, was uneventful and she was discharged well 14 days after the operation.

Two weeks later she suddenly developed severe,

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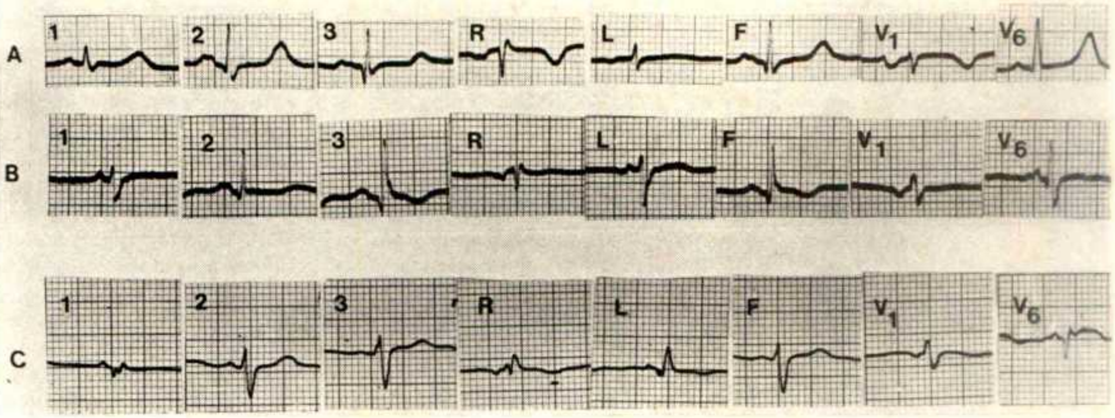

FIG. 1 *Electrocardiograms of Case 1: (A) before mitral valve replacement; (B) after mitral valve replacement; and (C) after repair of aneurysms. All traces were recorded at conventional paper speed (25 mm/s) and standardization (1 cm = 1 mV).*

gripping, central chest pain and lost consciousness for a few minutes. When she recovered the pain was still present in the central chest and radiated to the left arm. On examination she was cold and sweating, with a blood pressure of 90/50 mmHg. There was an increased left ventricular impulse and an apical pansystolic murmur (grade 2/4) radiating to the axilla. The electrocardiogram showed no evidence of any further myocardial infarction. The chest *x*-ray film, when compared with the earlier postoperative *x*-ray films, showed the development of a bulge of the left cardiac border (Fig. 2). The cardiac output rapidly improved and left ventriculography was performed. This showed minimal mitral regurgitation and a small true ventricular aneurysm on the posterolateral aspect of the left ventricle. There was also delayed filling of a false ventricular aneurysm which was situated higher up the posterolateral aspect of the left ventricle. It appeared to fill from the region of the atrioventricular groove.

It was decided to defer operation for repair of

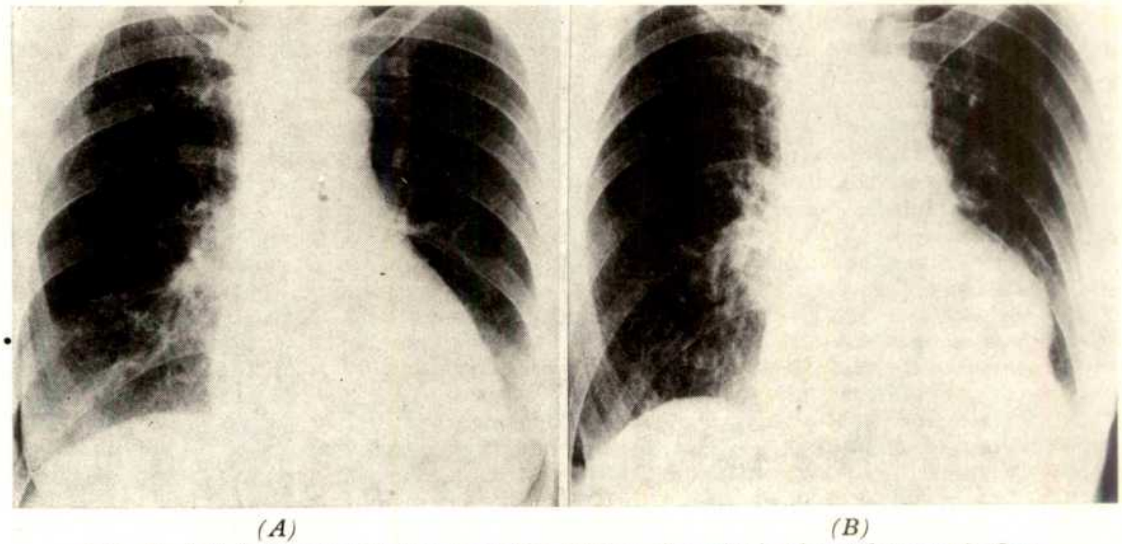
*(A)* *(B)*

FIG. 2 *(A) Posteroanterior chest* x-ray *film 10 days after mitral valve replacement in Case 1. (B) Posteroanterior chest* x-ray *film taken after the episode of severe chest pain in Case 1, showing the development of a bulge on the left cardiac border.*

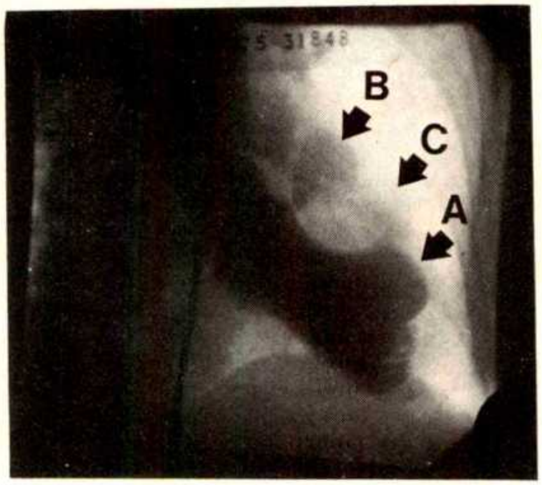

FIG. 3 *Left ventriculogram, in the anteroposterior projection, showing a true ventricular aneurysm (A) and a bilocular false ventricular aneurysm (B and C) in Case 1.*

these aneurysms because the tissues would be friable at this stage. She was, therefore, rested for one month after which left ventriculography was repeated. The true ventricular aneurysm was unchanged but the false aneurysm appeared to have extended to become bilocular (Fig. 3). Systolic jets from the posterior aspect of the atrioventricular groove into the false aneurysm were seen with each ventricular systole.

The patient was discharged for a further two months' rest at home and then readmitted for surgery. A third left ventriculography showed the appearances to be unchanged.

At operation (15 March 1975) the true aneurysm was found at the site of the previously sutured ventricular perforation and the area was plicated using 'teflon' reinforced sutures. The second aneurysm was confirmed to be a false aneurysm within the pericardium and containing thrombus. The prosthetic mitral valve was then exposed and no paravalvar leak was found. When the valve was removed a 2 mm hole was found in the left ventricle immediately below the level of the mitral ring at about the midpoint of where the posterior cusp had been. This communicated with the pericardial cavity. It was closed with a single reinforced suture and a new 27 mm Björk-Shiley prosthesis was inserted.

Recovery was again uneventful and there was no longer an apical systolic murmur. The electrocardiogram however showed pathological Q waves in leads I and AVL and left anterior hemiblock, in addition to the abnormal R wave in V1 previously noted (Fig. 1C). She was discharged 15 days after the operation and has remained well.

**Case 2**

A 62-year-old woman presented with mixed mitral and aortic valve disease. The valves were not calcified and the left ventricular cavity was moderately enlarged.

At operation (22 September 1975) slight mitral calcification and pronounced fusion of the subvalvar mechanism were found. The mitral and aortic valves were replaced by Starr-Edwards valves (size 4M in the mitral position). Cardiopulmonary bypass was ended but it was noted that blood was oozing from behind the heart and a haematoma was found in the posterior atrioventricular groove. Cardiopulmonary bypass was restarted. The mitral prosthesis was removed and a tear in the posterior atrioventricular groove was identified. This was repaired using 'teflon' reinforced mattress sutures and a 31 mm Björk-Shiley valve was then inserted into the mitral position. Uneventful recovery followed and there was no evidence of myocardial infarction.

Three months later she was readmitted with a month's history of severe dyspnoea. On examination she was in congestive heart failure and had an increased left ventricular impulse and pronounced left parasternal lift. The opening click of the Björk-Shiley mitral prosthesis was audible and there was a loud third heart sound. The Starr-Edwards aortic prosthesis made multiple opening sounds (Fig. 4) but no systolic murmur was audible in any area. Echocardiography, using a Smith Kline Ekoline 20 and a 2·25 MHz transducer focused at 5 cm, with Cambridge photographic strip chart recorder, showed apparently normal opening and closing of the mitral prosthesis, but indicated a large left ventricular stroke volume (Fig. 4), suggesting silent severe mitral paravalvar regurgitation. Aortography showed competence of the aortic prosthesis, which was then crossed with a pigtail catheter, on a guide-wire, in order to perform left ventriculography. This showed immediate opacification of the left atrium and, in addition, a rounded area behind the aorta (Fig. 5).

At reoperation the Björk-Shiley mitral valve appeared to be working normally but there was a hole in the left atrium, posterior and slightly to the left of the prosthesis, and this hole communicated with a false ventricular aneurysm in the back of the left ventricular wall.

The valve was excised and this showed the opening into the false aneurysm. The hole in the left atrium and the false aneurysm were closed. A new

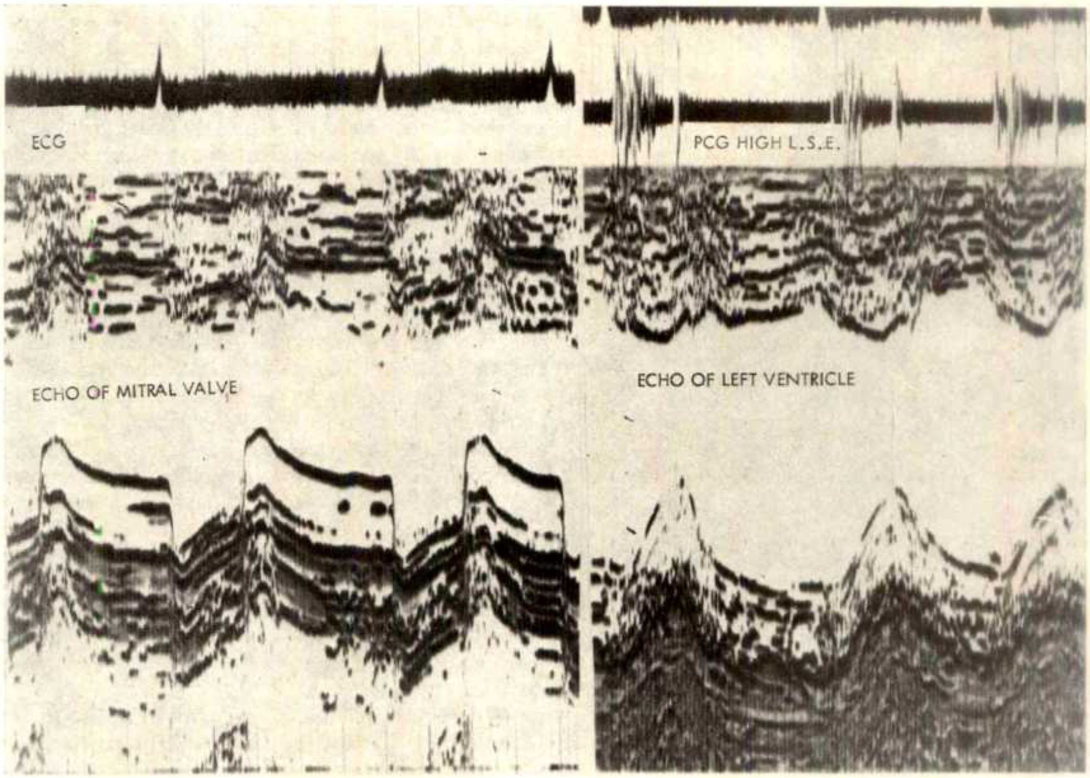

FIG. 4 *Echocardiogram of Björk-Shiley prosthesis in the mitral position in Case 2 showing normal opening and closing movement. Echocardiogram of the left ventricle in Case 2, showing pronounced synchronous, posterior wall and septal contraction. The phonocardiogram (PCG) shows multiple sounds caused by opening of the Starr-Edwards aortic prosthetic valve.*

25 mm Björk-Shiley prosthesis was then inserted and bypass was terminated. Recovery was uneventful and the electrocardiogram showed no evidence of myocardial infarction. She was discharged two weeks later with no evidence of cardiac failure.

### Discussion

Perforation of the ventricular wall in the region of the papillary muscles may occur during removal of the mitral valve (Treasure *et al.*, 1974; Zacharias *et al.*, 1975) particularly if this is being done under conditions of ischaemic arrest with a flaccid heart. Traction on the valve mechanism, to expose the papillary muscles for their division, causes inward tenting of the ventricular wall. Transection of the papillary muscle base then 'button-holes' the ventricular wall.

Treasure *et al.* (1974) state that perforation at the posterior aspect of the atrioventricular groove tends to occur when there is extensive calcification of the mitral annulus, when the cavity of the left ventricle is small, and when there has been previous surgery. None of these factors, however, was present in the two cases we report.

Rupture at either site may become evident immediately or there may be a delay of a few hours while the damaged tissue breaks down and then ruptures. There is often, therefore, no opportunity for the surgeon to try to repair the rupture, and even if the patient can be returned to the operating theatre an impossible situation may be found. Attempted repair of either variety of perforation carries with it grave danger of damage to adjacent coronary vessels, but this is particularly so with rupture into the atrioventricular groove. Here the pad of fat in the groove becomes infiltrated and swollen with blood and the overlying epicardial layer ruptures at multiple points so that the exact position of the underlying tear is impossible to locate. Deep sutures placed so as to reattach atrium to ventricle have to pass beneath both the circumflex artery and the coronary sinus, and either or both may be

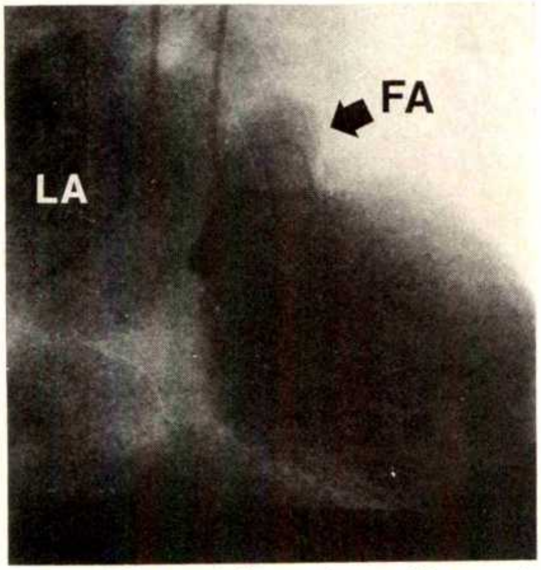

FIG. 5 *Left ventriculogram in a right anterior oblique projection. Contrast medium is shown to be filling the left atrium (LA) and there is an opacity behind the aortic root resulting from the false aneurysm (FA).*

compromised in the process. In a review of the published material Zacharias *et al.* (1975) found 19 cases of which 13 had been fatal.

Case 1 had rupture of the left ventricle at both sites. The perforation resulting from papillary muscle resection was evident before bypass had been completely terminated, and this probably accounts for the successful outcome. The rupture at the atrioventricular groove in this case was unusual in that it occurred one month after the operation and was small. It was probably caused by tissue necrosis around a single suture which had been placed too deeply. Because of pericardial adhesions this was not immediately fatal but resulted in the formation of a false ventricular aneurysm. This type of ventricular aneurysm tends to rupture (Vlodaver, Coe, and Edwards, 1975), but repair was electively delayed and left ventriculography was performed three times in the patient and appeared to be a safe procedure. It is thought that the delay allowed in this patient before further operation added considerably to the safety of the repair.

It is of interest that the pansystolic murmur in this patient appears to have been produced by blood jetting into the false aneurysm. Mitral regurgitation was of the trivial amount normal for a Björk-Shiley prosthesis and no paravalvar leak was present. Such a murmur has been reported in association with a false aneurysm occurring after myocardial infarction (MacNeil *et al.,* 1974), and Spellberg and O'Reilly (1972) found a similar murmur in the two cases of false ventricular aneurysm after mitral valve replacement that they report. Silent mitral regurgitation has been documented after myocardial infarction (Forrester *et al.,* 1971) and with prosthetic valves (Sanders, 1969). Silent mitral regurgitation was present in Case 2 and was unusual in that the route taken by the regurgitant jet was from the left ventricle to the false aneurysm and then to the left atrium. The echocardiogram showed increased synchronous, septal, and posterior wall contraction and was of considerable help in suggesting the presence of the mitral regurgitation, as Miller, Gibson, and Stephen (1973) have previously indicated.

In the second case the perforation of the left ventricle in the atrioventricular groove became evident as bypass was terminated and the immediate reinstitution of cardiopulmonary bypass, as in Case 1, was an important factor in the satisfactory outcome. The cause of the perforation in this case is uncertain. However, the tissues were noted to be friable and the size 4M Starr-Edwards prosthesis was a tight fit; this may have led to stretching and tearing the valve ring.

We believe that these two cases have shown that the correct approach to the problem of perforation of the ventricle in the atrioventricular groove is to remove the prosthetic valve and repair the tear from inside. In the two cases reported by Spellberg and O'Reilly (1972) the ventricular perforation and subsequent false aneurysm formation was thought to result from dissection of pericardial adhesions. However, the site of the hole in the left ventricle, in both cases, was very close to the posterior atrioventricular groove, and it seems likely that the mechanism is similar to that described in this report. We recommend that all patients who have repair of a ventricular perforation, particularly if this was in the atrioventricular groove, should have left ventriculography performed before discharge.

After a mitral valve replacement a pansystolic murmur may not represent mitral regurgitation but may be produced by a false ventricular aneurysm. In addition, mitral regurgitation, with or without a pansystolic murmur, may not be a simple paravalvar leak. We, therefore, recommend left ventriculography when surgery is contemplated, even in the presence of an aortic valve prosthesis, and even though echocardiography indicates mitral regurgitation.

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# Short left coronary artery trunk as a risk factor in the development of coronary atherosclerosis

## *Pathological study*

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*The relation between the length of the main left coronary artery and the degree of atherosclerosis in its branches was studied by postmortem examination in 204 subjects aged 20 to 90 years.*

*The findings suggest that in cases with a short main left coronary artery the atherosclerotic lesions in the anterior descending and circumflex branches appear earlier, progress faster at higher levels of severity, and lead more frequently to myocardial infarction, than in cases with a long left coronary artery trunk. In cases over the age of 50 years, where disease is expected to have developed, it was shown that the degree of atherosclerosis in the left anterior descending and circumflex branches was inversely related to the length of the main left coronary artery. The correlation coefficients were –0·527 and –0·428, respectively, and in either case a test for zero correlation was significant ($P<0{\cdot}001$).*

*The possible changes in the haemodynamic and mechanical conditions associated with the variations of the anatomical pattern of the coronary arteries and their influence in the development of atherosclerosis are discussed. It is suggested that the length of the main left coronary artery is a congenital anatomical and possibly hereditary factor influencing the rate of development of atherosclerosis in the branches of the main left coronary artery.*

The involvement of local mechanical and haemodynamic factors in the development of atherosclerosis of the coronary arteries is a generally accepted fact and the significance of such factors has been emphasized in recent publications (Glagov, 1972; Fry, 1972; Texon, 1974; Stehbens, 1975).

In a coronary arteriographic study from our department, we found that patients with a short main left coronary artery showed a high degree of atherosclerosis in its branches (Gazetopoulos *et al.*, 1976). This finding was attributed to the haemodynamic conditions associated with this anatomical pattern. However, the study was based on limited material derived mainly from patients suffering either from advanced coronary artery disease or valvular heart disease, who were candidates for heart surgery. Furthermore, these observations were indirect being based on coronary arteriographic appearance. For this reason a further study based on direct observation of a larger, randomly selected series of cases, was undertaken.

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This paper deals with pathological observations on the presence of atherosclerosis in relation to the length of the main left coronary artery.

## Subjects and methods

The coronary arteries were examined in 204 subjects (120 men and 84 women) aged 20 to 90 years who died suddenly or violently and were transferred to the Athens morgue for determination of the cause of death. Age and sex distribution are shown in Table 1. The cause of death was accident (76 cases), acute myocardial infarction (50 cases), cerebrovascular or vascular accident (42 cases), and miscellaneous diseases other than cardiovascular (36 cases).

The coronary arteries were dissected along the vessel's lumen and under direct observation the atheromatous lesions of the left anterior descending,

TABLE 1 *Age and sex distribution*

| *Age (y)* | *Men*<br>*Short** | <br>*Long†* | <br>*Total* | *Women*<br>*Short** | <br>*Long†* | <br>*Total* |
|---|---|---|---|---|---|---|
| 20–29 | 9 | 4 | 13 | 3 | 3 | 6 |
| 30–39 | 6 | 5 | 11 | 5 | 2 | 7 |
| 40–49 | 8 | 9 | 17 | 2 | 5 | 7 |
| 50–59 | 14 | 7 | 21 | 5 | 7 | 12 |
| 60–69 | 15 | 9 | 24 | 9 | 8 | 17 |
| 70–79 | 13 | 7 | 20 | 12 | 12 | 24 |
| 80–89 | 9 | 5 | 14 | 6 | 5 | 11 |
| Total | 74 | 46 | 120 | 42 | 42 | 84 |

*Number of cases with a left coronary artery trunk of 11 mm or shorter.
†Number of cases with a left coronary artery trunk of 12 mm or longer.

circumflex, and right coronary artery were classified in the following five degrees of severity.

0 : No atherosclerosis present.
I : Atherosclerosis resulting in luminal narrowing of less than 25 per cent.
II : Atherosclerosis resulting in luminal narrowing between 25 and 50 per cent.
III : Atherosclerosis resulting in luminal narrowing between 50 and 75 per cent.
IV : Atherosclerosis resulting in narrowing from 75 per cent up to complete occlusion of the lumen.

Where multiple lesions were present in any of the above major branches, the most severe one was taken into consideration.

The length of the main left coronary artery, the heart's weight, the maximum thickness of the free left ventricular wall and the height of each individual were also measured.

Measurements and evaluations were done by at least two independent observers. Whenever there was disagreement, the average of the estimates was taken into consideration.

## Statistical analysis

Since data regarding severity of atherosclerosis were grouped in five grades those of the main left coronary artery's length were also grouped, and correlation coefficients were estimated by a grouped frequency table (Hill, 1971). Differences between mean values were evaluated by the Student's t test. Differences between proportions were assessed for significance by using the $\chi^2$ test.

## Results

The length of the left coronary artery trunk ranged from 0 to 24 mm, mean 11·02 ±4·5 mm.

Fig. 1 shows the average degree of atherosclerosis in the two branches of the left coronary artery as evolving with age in each sex group. Data from cases with a left coronary artery trunk longer than the above-mentioned mean length are shown separately from those with a shorter one. The distribution of cases with a short and with a long left coronary artery per age and sex is given in Table 1. As seen in Fig. 1, with advancing age, particularly after the fifth decade of life, there is a dissociation between the curves of severity of atherosclerosis, with an early rise and a higher rate of development in cases with a short left coronary artery trunk.

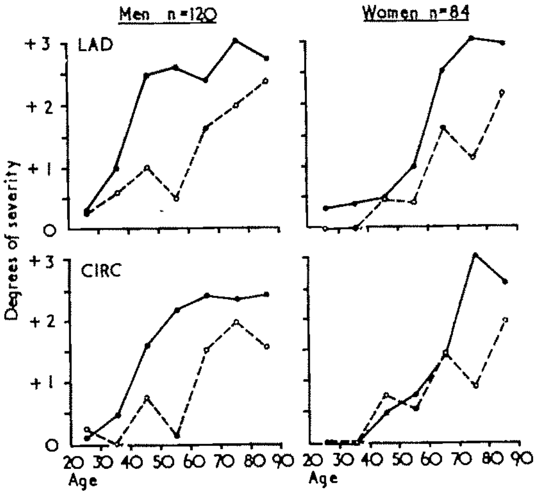

FIG. 1 *Average degree of coronary atherosclerosis related to age and sex group in the left anterior descending (LAD) and circumflex (CIRC) branches of the left coronary artery. There is a gap with advancing age between the degree of atherosclerosis in cases with a left coronary artery trunk of 11 mm or shorter (solid lines) as compared with that in cases with a left coronary artery trunk of 12 mm or more (interrupted lines).*

Table 2 shows the mean length of the left coronary artery trunk corresponding to each degree of atherosclerosis in the left anterior descending and circumflex branches. Since the incidence of coronary atherosclerosis is low for the young Greek population studied, only cases over the age of 50 were included in the Table. It is seen that the higher the degree of atherosclerosis, the shorter is the corresponding mean length of the main left coronary artery. After grouping data for moderate (grades I and II) and severe (grade III and IV) atherosclerosis, differences between the

TABLE 2 *Length of left coronary artery trunk (mm) and degree of atherosclerosis*

| *Degree of atherosclerosis* | *Left anterior descending* *Mean length* | *±1 SD* | *No.* | *P<* | *Circumflex* *Mean length* | *±1 SD* | *No.* | *P<* |
|---|---|---|---|---|---|---|---|---|
| 0 | 15·33 | 3·84 | 24 | | 13·72 | 5·17 | 39 | |
| I | 12·69 | 4·74 | 29 | 0·001 | 11·48 | 3·51 | 23 | 0·025 |
| II | 10·38 | 4·21 | 23 | | 11·40 | 5·21 | 20 | |
| I+II | 11·85 | 4·61 | 52 | | 11·44 | 4·38 | 43 | |
| III | 9·17 | 3·9 | 30 | 0·001 | 9·0 | 4·12 | 35 | 0·025 |
| IV | 8·32 | 4·15 | 37 | | 8·65 | 3·73 | 26 | |
| III+IV | 8·70 | 4·06 | 67 | | 8·85 | 3·97 | 51 | |

corresponding mean lengths of the left coronary artery trunk were significant.

In Fig. 2 and 3 the distribution of cases included in Table 2 is shown, as well as the corresponding regression lines and their 95 per cent confidence limits. The degree of severity of atherosclerosis in the left anterior descending branch (Fig. 2) was inversely related to the length of the main left coronary artery. The correlation coefficient was −0·527, differing from zero at a significant level of probability (P < 0·001).

The degree of severity of atherosclerosis in the circumflex branch (Fig. 3) was also inversely related to the length of the main left coronary artery. The correlation coefficient was −0·428 (P < 0·001). The relation between the length of the main left coronary artery and the degree of atherosclerosis in the right coronary artery was also studied. As expected, no significant correlation was found between these two variables (r = 0·166, P > 0·05). Similarly, no relation was found between the main left coronary artery's length and the heart's weight, thickness of the free left ventricular wall, and the individual's height, age, and sex.

Table 3 shows the number of patients who died from myocardial infarction and those who died from other causes in relation to the length of the left coronary artery trunk. In the group of cases without myocardial infarction the ratio of persons with either short or long trunks is 1:1, while in the group of cases with myocardial infarction the ratio is about 3:1. This difference was significant (0·01 < P < 0·02). The mean length of the left coronary artery trunk in cases with myocardial infarction aged over 50 years (N = 45) was 9·9 ± 1 mm, while in the cases without evidence of atherosclerosis (0 grade) in left coronary artery branches in the same age group (N = 20) was 15·1 ± 3·86 mm. The difference between the above two means was highly significant (P < 0·001).

## Discussion

Our previous study based on coronary arteriographic findings (Gazetopoulos *et al.*, 1976) and the present one based on pathological observations suggest that a long main left coronary artery exerts some protective action against the development of atherosclerosis in its branches. The mechanisms involved seem likely to be related to modification of mechanical and hydraulic factors resulting from difference in the length of the left coronary artery trunk.

That local mechanical and haemodynamic factors may be relevant to the development of atherosclerosis is indicated by the fact that the greatest atherogenic effect tends to appear in sites of predilection, such as bifurcations, branchings, bends, and narrowings, where mechanical stresses are likely to be higher (Schlesinger and Zoll, 1941; Willis, 1954; Duguid and Robertson, 1957; Schwartz and Mitchell, 1962; Pitt *et al.*, 1963; Caro, Fitz-Gerald, and Schroter, 1969).

Increased pressure (Clawson, 1939; Glagov, Rowley, and Kohut, 1961; Kannel, Schwartz, and McNamara, 1969), increased flow rate (Fox and Hugh, 1966; Gyurko and Szabo, 1969), several variables related to changes of pressure and flow (Sako, 1962; Scharfstein, Gutstein, and Lewis, 1963; Glagov, 1972; Texon, 1974), and systolic motion resulting in curving of the coronary vessels (Fulton, 1965; Glagov, 1972) have been suggested as factors creating mechanical conditions initiating or accelerating the development of atherosclerosis in these sites of predilection.

Poiseuille's law relates the drop in pressure (ΔP) along a vessel's lumen to its length (L):

$$\Delta P = \frac{8L}{\pi r^4} . F . v \text{ (r: radius, F: flow, v: viscosity).}$$

Furthermore, as provided by the above formula flow rate (F) is inversely proportional to a vessel's length. Though Poiseulle's law cannot be quantitatively applied to the circulatory system, it is reasonable to suggest that a long main left coronary artery, by decreasing the pressure and probably flow velocity, decreases the forces acting on its branching area and beyond it.

Another factor that could be involved is the

TABLE 3 *Length of left coronary artery trunk and relation to death from myocardial infarction*

| *Cause of death* | *Short* LCAT (No. of cases)* | *Long† LCAT* |
|---|---|---|
| Myocardial infarction | 33 | 12 |
| Other than myocardial infarction | 50 | 48 |

$\chi^2 = 6{\cdot}3$
$0{\cdot}01 < P < 0{\cdot}02$

*11 mm or shorter
†12 mm or longer.
LCAT = Left coronary artery trunk.

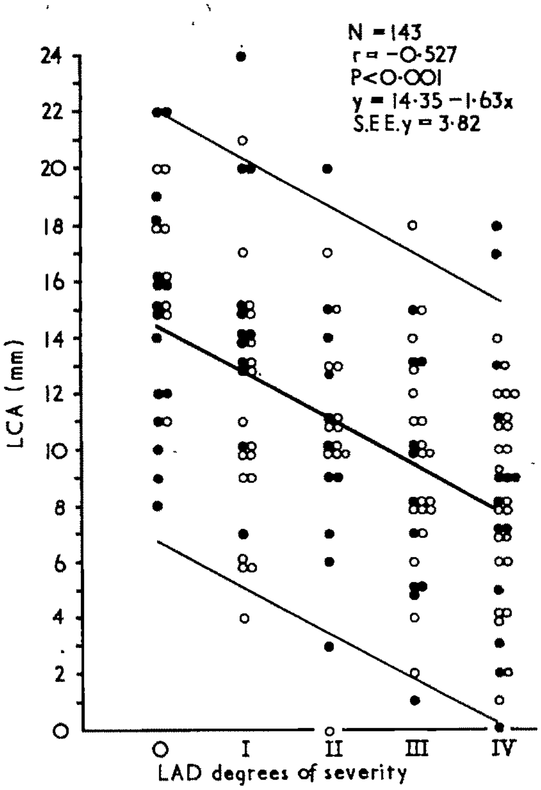

FIG. 2 *Relation between the length of the left coronary artery trunk and the degree of severity of atherosclerosis in the left anterior descending branch in men (open circles) and women (closed circles) aged over 50 years. The regression line is paralleled by the 95 per cent confidence limits (two Standard Errors of Estimate). The correlation coefficient (r) differs significantly from zero.*

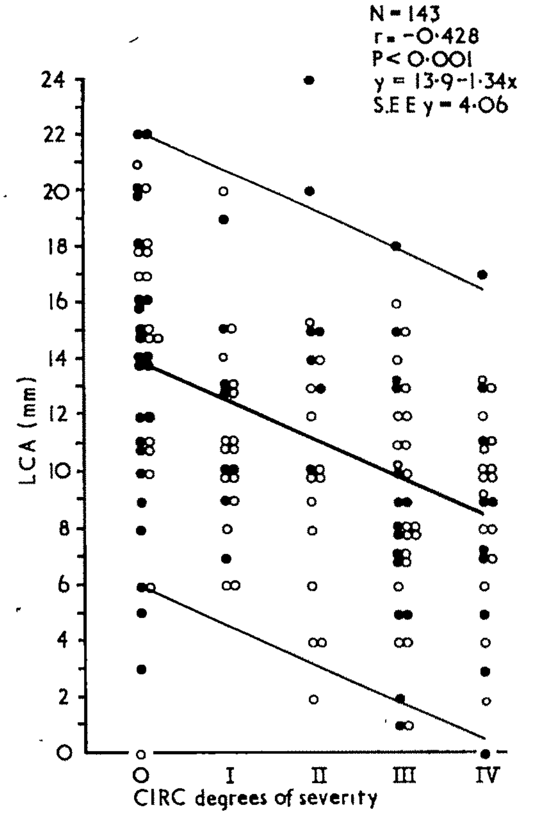

FIG. 3 *Relation between the length of the left coronary artery trunk and the degree of atherosclerosis in the circumflex branch in men (open circles) and women (closed circles) aged over 50 years. The regression line is paralleled by the 95 per cent confidence limits (2 Standard Errors of Estimate). The correlation coefficient (r) differs significantly from zero.*

vessel's compliance which is proportional to the change of its volume determined by the vessel's calibre and length. Thus, it is likely that the main left coronary artery would absorb part of the systolic pressure and flow wave and return it later to a degree depending on the vessel's length. This damping effect, exercised at the bifurcation area, would decrease the peak systolic pressure, pulse pressure, peak flow velocity, and rate of change in flow velocity, factors that have been implicated in the development of atherosclerosis (Texon, 1974).

Sites of bending, knuckling, and narrowing of the coronary arteries during the heart's action are also subject to atherogenic effect (Fulton, 1965; Glagov, 1972). The initial part ('neck') of the left anterior descending tethered proximally by its origin from the main left coronary artery and distally by its first myocardial branch is subject to a higher risk of bending and knuckling than the epicardial portion of the other coronary arteries (Fulton, 1965; Lewis *et al.,* 1970). Therefore, it is conceivable that the shorter the left coronary artery trunk, the longer the free unattached part of the left anterior descending branch would be. Thus, during systole it would become more bent or kinked than if it were a short one, as in cases with a long left coronary artery.

Even without considering the possibility of a lumen's narrowing during systolic kinking, the formed curve alone is expected to modify hydraulic conditions across the lumen of the curved vessel. The centrifugal forces applied at the curved area would increase the lateral pressure along the outer wall, while at the same time they would diminish the pressure along the inner wall (Texon, 1957). On the other hand, in a curved vessel, axial layers of high flow velocity are impinging on the outer wall (Glagov, 1972). Increased flow rate, according to Fry (1968, 1969) causes injury or detachment of the endothelium undergoing the stress of the shearing forces, or according to Texon (1963, 1972) preatherosclerotic intimal proliferation by 'suction effect' at low pressure areas produced by the increased flow.

The above-mentioned factors, i.e. systolic bending and curving of the left anterior descending, can serve as a possible explanation as to why this vessel and especially its first free portion is frequently involved by atherosclerosis (Schlesinger and Zoll, 1941; Pitt *et al.,* 1963; Vlodaver and Edwards, 1974) and how this predilection can be exaggerated when the left coronary artery trunk is short.

Relation between a short left coronary artery trunk and coronary atherosclerosis is a finding not previously reported. The only relevant hint was presented by Lewis *et al.* (1970) where in 11 out of 12 cases with electrocardiographic evidence of a left bundle-branch block a main left coronary artery trunk, less than 6 mm long, was found by coronary arteriographic means. This was attributed to inadequacy in blood supply to the left bundle, resulting from increased systolic kinking caused by the short left coronary artery trunk. Though confirmation by other investigators (Hamby, Tabrah, and Gupta, 1973) was not so extensive, in our previous report all 4 cases with left bundle-branch block had a short main left coronary artery (Gazetopoulos *et al.,* 1976).

The scatter of our data around the regression line is large, as can be seen in Fig. 2 and 3, and the magnitude of correlation is not impressive. But it would be surprising if this were not so, in view of the number of other factors involved in the development of coronary artery disease. However, it must be noted that mechanical and haemodynamic changes deriving from anatomical variations in the structure of the arterial tree have been proposed as basic factors in the initiation of atherosclerosis. The rest of the known predisposing factors have been considered as secondary or simply modifying the atherogenic process (Altschule, 1974; Texon, 1974).

The present study enhances the previous findings (Gazetopoulos *et al.,* 1976), that the length of the main left coronary artery is an anatomical factor which may influence the rate of development of atheromatosis on its branches. Since anatomical structure and distribution of the coronary arteries is possibly determined by heredity, as are other morphological characteristics, the length of the main left coronary artery could be considered a heriditary factor predisposing to coronary artery disease.

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# Use of noninvasive methods in evaluation of left ventricular performance in coronary artery disease

## *II: Change in systolic time intervals after coronary artery bypass in patients with stable angina*

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*Serial recording of systolic time intervals (STI) was used to assess changes in left ventricular (LV) function in 92 patients with stable angina undergoing coronary angiography and LV cineangiography. On the basis of angiography, patients were placed in the following study groups: mild or absent coronary artery disease group —21 patients with less than 70 per cent occlusion of all coronary arteries, considered to have non-significant coronary artery disease and not needing bypass surgery; surgical bypass group—52 patients with evidence of significant ($>70\%$) obstruction of at least one coronary artery who underwent myocardial revascularization; and medical group—19 patients with evidence of significant coronary artery disease not undergoing bypass surgery.*

*Measured STI, corrected for heart rate and sex, were expressed as indices. No significant differences were noted in the mean STI from the time of initial evaluation to second evaluation 3 to 6 months later in either the mild or absent coronary artery disease patients or the medical group. In the surgical bypass group, however, serial studies at initial angiographic evaluation and 3 to 6 months after bypass surgery showed a shortened pre-ejection period (PEP) from $150\pm20$ to $142\pm16$ ms ($P<0{\cdot}001$), prolonged left ventricular ejection time (LVET) from $396\pm21$ to $409\pm14$ ms ($P<0{\cdot}02$), and decreased PEP/LVET from $0{\cdot}45\pm0{\cdot}11$ to $0{\cdot}40\pm0{\cdot}07$ ($P<0{\cdot}02$). Paired data analysis of the three groups also showed a significant change only within the surgical bypass group from initial to final study, with a shortened PEP ($P<0{\cdot}002$), prolonged LVET ($P<0{\cdot}001$), and decreased PEP/LVET ($P<0{\cdot}001$).*

*These data suggest improvement in LV function in patients with significant coronary artery disease within a few months of myocardial revascularization, without demonstrable change in STI in those patients with coronary artery disease not subjected to revascularization.*

Myocardial revascularization procedures have two important goals: (1) to relieve anginal pain and (2) to maintain myocardial viability and possibly to improve left ventricular (LV) performance (Johnson and Kayser, 1963; Kirklin, 1973). It is well established that such revascularization procedures relieve anginal pain in most patients with significant coronary artery obstruction (Mitchel *et al.*, 1970; Spencer *et al.*, 1971; Morris *et al.*, 1972). Long-term follow-up studies have provided conflicting results as to the effect of surgery upon LV performance, but some have shown that, with maintained graft patency, performance may improve (Saltiel *et al.*, 1970; Manley *et al.*, 1970; Manley and Johnson, 1972; Chatterjee *et al.*, 1972; Griffith *et al.*, 1973).

The most direct means of serially evaluating LV function after bypass has been by LV catheterization and cineangiography (Rutherford *et al.*, 1972; Hammermeister *et al.*, 1974). This approach has not been routinely used, however, because of such considerations as lack of symptoms, the minor but definite risk that catheterization holds, or because of refusal of the patient to submit to re-examination

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by this technique.

It is clear that reliable information about LV performance obtained non-invasively would be valuable in the follow-up of patients with coronary artery disease after bypass procedures because this approach would allow convenient and frequent study without risk to the patient. One such approach involves the use of indirectly determined systolic time intervals (STI), which have been shown reliably to reflect angiographic and haemodynamic changes in LV performance (Weissler, Harris, and White, 1963; Weissler, Harris, and Schoenfeld, 1968; Garrard, Weissler, and Dodge, 1970; Martin *et al.*, 1971). STI have been shown previously to be useful in serially assessing change in performance in coronary artery disease (Diamant and Killip, 1970; Pouget *et al.*, 1971; Hodges *et al.*, 1972).

This study was designed to investigate the effect of aortocoronary bypass on LV performance in patients with stable angina using serial STI determination, and to compare changes in this surgical group with serial STI in a group of patients with signicant coronary artery disease not subject to surgical intervention.

TABLE 1 *Patient studies in each group with exclusions after initiation of study*

| *Group* | *No. of patients* | *No. excluded* | *Reason for exclusion* |
|---|---|---|---|
| 0V | 25 | 4 | 4-NR |
| CADm: | | | |
| 1V | 10 | 3 | 2-NR, 1-D |
| 2V | 6 | 1 | 1-NR |
| 3V | 7 | — | — |
| Total CADm | 23 | 4 | 3-NR, 1-D |
| CADs: | | | |
| 1V | 15 | 2 | 1-NR, 1-D |
| 2V | 29 | 7 | 6-NR, 1-D |
| 3V | 21 | 4 | 3-NR, 1-D |
| Total CADs | 65 | 13 | 10-NR, 3-D |
| Total | 113 | 21 | 17-NR, 4-D |

*Abbreviations:* 0V=mild or absent coronary artery obstruction (<70% occlusion); CADm=significant coronary artery disease treated medically (>70% occlusion); CADs=significant coronary artery disease treated surgically (>70% occlusion); 1V=one-vessel disease; 2V=two-vessel disease; 3V=three-vessel disease; NR=did not return for follow-up study. D=died before follow-up period.

## Subjects and methods

One hundred and thirteen patients with chest pain suggesting possible coronary artery disease who were evaluated in the catheterization laboratory of Rush-Presbyterian-St. Luke's Medical Center underwent STI determination immediately before coronary and left ventricular cineangiography. Of these, 92 who completed re-evaluation by STI from 3 to 6 months after initial study were included in the assessment (Table 1).

### Cineangiographic study

All patients underwent selective coronary and left ventricular cineangiography according to the techniques of Sones and Shirey (1962) and Lehman, Debbas, and Boyle (1963), respectively. Angiographic evidence of greater than 70 per cent arterial obstruction of any major coronary artery was considered to document significant vessel disease (Wégria *et al.*, 1949), and a significant left main coronary artery lesion was considered to represent two vessel disease.

### Systolic time interval determination

STI were measured from the simultaneous recording of the electrocardiogram, phonocardiogram, and indirect carotid artery pulse tracing by the Elema-Schonander Mingograf ink-jet recording system at a paper speed of 100 mm/s, using previously described techniques (Weissler and Garrard, 1971; Meng *et al.*, 1975). The STI determined included total electromechanical systole ($Q\text{-}S_2$); left ventricular ejection time (LVET); and pre-ejection period (PEP), obtained by subtracting LVET from $Q\text{-}S_2$ (Weissler and Garrard, 1971).The STI were then corrected for heart rate and sex according to the regression equations of Weissler, thus yielding the indices $Q\text{-}S_2I$, PEPI, LVETI (Garrard *et al.*, 1970). The indices were used as the final determinants of values, with the exception of the PEP/LVET ratio which was determined by dividing the uncorrected values of these time intervals.

### Patient groups

Optimal management for each patient was determined jointly by cardiologists and cardiovascular surgeons after consideration of clinical, angiographic, and haemodynamic data according to commonly accepted criteria. Specifically, congestive heart failure was not considered a strict contraindication to bypass surgery. Those patients satisfying the criteria received surgery, and all other patients received medical management.

On the basis of the results of angiography, three selected groups were considered for evaluation.

### (1) Mild or absent coronary artery obstruction

These patients were found to have less than 70 per cent obstruction of all coronary arteries, and thus did not need bypass procedures (21 patients).

**(2) Coronary artery disease treated medically** These patients had significant (>70%) obstruction in at least one coronary artery, and were treated medically (19 patients: 11 of these patients had poor distal perfusion, and 8 were considered not to have severe enough symptoms to warrant surgery).

**(3) Coronary artery disease treated surgically** These patients had significant (>70%) obstruction in at least one coronary artery, and were treated by myocardial revascularization, which was performed by either reverse saphenous vein or internal mammary artery grafting (52 patients). Gas endarterectomy was infrequently used, and 2 cases required left ventricular myocardial plastic procedures. The vessels bypassed in relation to the number of vessels with significant obstruction are listed in Table 2.

Groups 2 and 3 were further subdivided according to number of coronary arteries significantly obstructed (one, two, or three vessels = 1V, 2V, and 3V).

## Serial studies

STI were performed initially at time of angiography (Period 1), and again 3 to 6 months later (Period 2). Surgical bypass was performed within two weeks of angiography and initial STI determination.

TABLE 2 *Bypass procedures performed*

| *Group* | *No. of patients* | *Vessels bypassed* *1* | *2* | *3* |
|---|---|---|---|---|
| 1V | 13 | 13 | | |
| 2V | 22 | 7* | 15 | |
| 3V | 17 | 3 | 12 | 2 |
| Total | 52 | 23 | 27 | 2 |

*One patient had ventricular septal defect repair, and one patient had resection left ventricular aneurysm.

*Abbreviations:* 1V = one-vessel disease; 2V = two-vessel disease; 3V = three-vessel disease.

Data analysis was performed with the aid of an Olivetti Underwood Programma 101 computer and Monroe Electronics Programmable Statistical Calculator, using Student's t test, both independent and $\chi^2$ analysis.

## Results

### Clinical data (Table 3)

After the initial evaluation of 113 patients, 21 did not undergo serial evaluation for the reasons shown in Table 1. There was no difference in mean age in

TABLE 3 *Clinical evaluation of patient groups in study (92 patients)*

| *Group* | *No. of patients* | *Age (y)** | *Period* | *Clinical findings* | | *Medications* | | | *Prior acute myocardial infarctions* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *AP* | *CHF* | *P* | *D* | *AR* | *No. of pts.* | *No. of infarcts* |
| 0V | 21 | 48 ± 9 | 1 | 21 | 3 | 2 | 3 | 0 | 1 | 4 |
| | | | 2 | 13 | 7 | 5 | 2 | 0 | | |
| CADm: | | | | | | | | | | |
| 1V | 7 | 50 ± 6 | 1 | 7 | 0 | 1 | 2 | 0 | 4 | 5 |
| | | | 2 | 7 | 0 | 0 | 0 | 1 | | |
| 2V | 5 | 56 ± 7 | 1 | 5 | 1 | 0 | 0 | 0 | 4 | 5 |
| | | | 2 | 5 | 1 | 3 | 2 | 0 | | |
| 3V | 7 | 52 ± 10 | 1 | 7 | 2 | 1 | 2 | 1 | 4 | 8 |
| | | | 2 | 6 | 5 | 3 | 4 | 1 | | |
| Total CADm | 19 | 52 ± 8 | 1 | 19 | 3 | 2 | 4 | 1 | 13 | 22 |
| | | | 2 | 18 | 6 | 6 | 2 | 2 | | |
| CADs: | | | | | | | | | | |
| 1V | 13 | 52 ± 6 | 1 | 13 | 1 | 1 | 2 | 0 | 5 | 6 |
| | | | 2 | 0 | 0 | 0 | 0 | 1 | | |
| 2V | 22 | 52 ± 7 | 1 | 22 | 5 | 1 | 5 | 4 | 12 | 15 |
| | | | 2 | 4 | 1 | 1 | 6 | 2 | | |
| 3V | 17 | 54 ± 8 | 1 | 17 | 4 | 2 | 2 | 1 | 12 | 19 |
| | | | 2 | 1 | 2 | 0 | 7 | 2 | | |
| Total CADs | 52 | 53 ± 7 | 1 | 52 | 10 | 4 | 9 | 5 | 29 | 40 |
| | | | 2 | 5 | 4 | 1 | 13 | 5 | | |

*Mean ± 1 SD.

*Abbreviations*: AP = anginal pain; CHF = congestive heart failure; P = propranolol; D = digitalis; AR = antiarrhythmics (quinidine or procainamide). For other abbreviations see footnote to Table 1.

all 3 groups. All patients were admitted to the study because of anginal symptoms at the time of initial evaluation. At the time of follow-up, 62 per cent of the mild or absent coronary artery disease group still had anginal symptoms as did 95 per cent of the medically treated group, but only 10 per cent of the surgical bypass group complained of angina. Clinical evidence of congestive heart failure increased slightly in the mild or absent, and medically treated groups but decreased in the surgical bypass group.

The percentage of patients in each group receiving digitalis initially varied from 14 to 21 per cent. At follow-up, there was a decrease in this percentage to 10 per cent in both the mild or absent, and medically treated groups. The surgical bypass group, however, increased its digitalis usage to 25 per cent of patients. Propranolol was being administered initially to 4 to 10 per cent of patients in each group. Its use increased to 24 per cent and 30 per cent in the mild or absent, and medically treated groups, respectively, and decreased to 2 per cent in the surgical bypass group. Antiarrhythmic drugs, either quinidine or procainamide, were not administered to the mild or absent coronary artery disease group, but in the medically treated group were administered to 1 patient initially and to 2 patients at follow-up. Five patients in the surgical bypass group received these agents both at the beginning and end of the study.

Evidence for previous infarction was found in 5 per cent of the mild or absent group, 68 per cent of the medically treated group and 56 per cent of the surgical bypass group. None of the patients in the final study groups developed infarction during the course of the study.

### Changes in mean STI values: intragroup comparisons (Table 4)

Comparison of mean values between Periods 1 and 2 for each group and subgroup showed no significant change for the mild or absent coronary artery disease group or the medically treated group. The surgical bypass group, however, showed a significantly increased LVETI from 396 ±21 ms to 409 ±14 ms ($P < 0{\cdot}001$), decreased PEPI from 150 ±20 to 142 ±16 ms ($P < 0{\cdot}02$), and a decreased PEP/LVET from 0·45 ±0·11 to 0·40 ±0·07 ($P < 0{\cdot}02$). When surgical subgroups were studied, LVETI increased significantly in 2V and 3V patients, and PEPI and PEP/LVET decreased significantly in 2V patients.

Paired t test analysis showed no significant change in the absent or mild disease group and the medically treated groups, but a significant increase in LVET ($P < 0{\cdot}001$) and decrease in PEPI ($P < 0{\cdot}002$) and PEP/LVET ($P < 0{\cdot}001$) in the surgical bypass group (Table 5).

### Intergroup comparisons: period 1

Comparison between the medically treated group and the mild or absent coronary artery disease groups showed a significantly greater PEP/LVET in the medically treated group ($P < 0{\cdot}05$). There were no differences when medical subgroups were compared with the mild or absent coronary artery disease group. The surgical bypass group had a shorter LVETI and greater PEP/LVET than the absent or mild group ($P < 0{\cdot}05$) for both comparisons, with significant differences in subgroups also (Table 4). There was no significant difference between the medical group, and surgical bypass groups in any STI.

### Intergroup comparisons: period 2

No significant differences were found between the 3 groups.

## Discussion

Our results show the considerable improvement in symptoms of angina after revascularization seen in other studies (Griffith *et al.*, 1973; Hammermeister *et al.*, 1974). The findings of improvement in STI in the 3 to 6 month follow-up after bypass surgery also suggests an improvement in myocardial function.

It would not be expected that patients in the medically treated group would improve LV function at follow-up evaluation, as is shown by the lack of significant improvement of STI in that group. It is true, however, that had this patient group been larger, significant changes might have been realized. The absent or mild disease group, with lack of significant coronary artery disease (less than 70% occlusion of any major vessel), showed insignificant change in serial STI studies. It might be argued that this group could in fact manifest ischaemia as a result of small vessel disease, but initial LVETI and PEP/LVET in this group were significantly less abnormal than those of the surgical group during the initial study. In serial study, the STI in the surgical bypass group returned to normal significantly more than either the mild or absent coronary artery disease group or the medical group. This is because of the more abnormal initial values in the surgical bypass group. Individual group mean STI values appeared to reflect myocardial function abnormalities by objective measurement of left ventricular function, as has been

TABLE 4 *Systolic time intervals*

| *Group* | *No. of patients* | *Period* | *Q-$S_2$I* (ms)* | *PEPI* (ms)* | *LVETI* (ms)* | *PEP/LVET** |
|---|---|---|---|---|---|---|
| 0V | 21 | 1 | 555 ± 19 | 140 ± 20 | 408 ± 21 | 0·38 ± 0·07 |
| | | 2 | 548 ± 17 | 143 ± 21 | 414 ± 17 | 0·40 ± 0·09 |
| CADm: | | | | | | |
| 1V | 7 | 1 | 543 ± 24 | 143 ± 20 | 399 ± 10 | 0·42 ± 0·09 |
| | | 2 | 555 ± 23 | 146 ± 13 | 409 ± 16 | 0·40 ± 0·05 |
| 2V | 5 | 1 | 559 ± 23 | 151 ± 16 | 393 ± 32 | 0·47 ± 0·11 |
| | | 2 | 563 ± 16 | 150 ± 25 | 412 ± 16 | 0·42 ± 0·11 |
| 3V | 7 | 1 | 543 ± 21 | 148 ± 22 | 394 ± 22 | 0·46 ± 0·12 |
| | | 2 | 542 ± 16 | 141 ± 28 | 400 ± 22 | 0·41 ± 0·12 |
| Total CADm | 19 | 1 | 547 ± 23 | 147 ± 19 | 396 ± 21 | 0·44 ± 0·10 |
| | | 2 | 552 ± 20 | 146 ± 22 | 406 ± 18 | 0·41 ± 0·09 |
| CADs: | | | | | | |
| 1V | 13 | 1 | 542 ± 25 | 144 ± 19 | 398 ± 16 | 0·40 ± 0·09 |
| | | 2 | 554 ± 13 | 143 ± 11 | 411 ± 12 | 0·40 ± 0·05 |
| 2V | 22 | 1 | 547 ± 25 | 148 ± 18 | 398 ± 25 | 0·45 ± 0·11 |
| | | 2 | 548 ± 18 | 138 ± 17 | 411 ± 13 | 0·38 ± 0·07 |
| 3V | 17 | 1 | 548 ± 23 | 156 ± 20 | 392 ± 19 | 0·48 ± 0·11 |
| | | 2 | 553 ± 21 | 147 ± 17 | 406 ± 17 | 0·43 ± 0·08 |
| Total CADs | 52 | 1 | 546 ± 24 | 150 ± 20 | 396 ± 21 | 0·45 ± 0·11 |
| | | 2 | 551 ± 18 | 142 ± 16 | 409 ± 14 | 0·40 ± 0·07 |

*Significant differences in mean values (2-tailed t test)***

| | *Q-$S_2$I* (ms)* | *PEPI* (ms)* | *LVETI* (ms)* | *PEP/LVET** |
|---|---|---|---|---|
| *Period 1 vs. Period 2* | | | | |
| 0V | All not significant | | | |
| CADm | All not significant | | | |
| CAD: | | | | |
| 1V | NS | NS | NS | NS |
| 2V | NS | <0·05 | <0·05 | <0·05 |
| 3V | NS | NS | <0·05 | NS |
| Total CADs | NS | <0·02 | <0·001 | <0·02 |
| *Period 1* | | | | |
| CADm vs. CADs | All not significant | | | |
| CADm vs. 0V | All not significant | | | |
| CADs vs. 0V: | | | | |
| 1V vs. 0V | NS | NS | NS | NS |
| 2V vs. 0V | NS | NS | NS | <0·025 |
| 3V vs. 0V | NS | <0·02 | <0·02 | <0·005 |
| Total CADs vs. 0V: | NS | NS | <0·05 | <0·05 |
| *Period 2* | | | | |
| CADm vs. CADs | All not significant | | | |
| CADm vs. 0V | All not significant | | | |
| CADs vs. 0V | All not significant | | | |

*Mean values ± 1 SD.
**P values.

*Abbreviations:* Q-$S_2$I = total electromechanical systole index; PEPI = pre-ejection period index; LVETI = left ventricular ejection time index; PEP/LVET = ratio of uncorrected intervals; NS = not significant.

TABLE 5 *Changes in systolic time intervals from Period 1 to Period 2**

| *Group* | *No. of patients* | *PEPI** (ms)* | *LVETI** (ms)* | *Q-S21** (ms)* | *PEP/LVET*** |
|---|---|---|---|---|---|
| OV | 21 | −3·33<br>NS | +5·66<br>NS | +6·87<br>NS | +1·52<br>NS |
| CADm | 19 | −1·47<br>NS | +5·68<br>NS | +5·16<br>NS | −3·47<br>NS |
| CADs | 52 | −7·71<br>P<0·002 | +12·81<br>P<0·001 | +5·21<br>NS | −4·48<br>P<0·001 |

*Paired t test.
**Mean change of paired values.
*Abbreviations:* For abbreviations, see previous tables.

previously shown. There was, however, considerable overlap in individual STI values, indicating that one determination may not allow exact quantification of the degree of left ventricular dysfunction. A more valuable and reliable use of STI may be examination of serial changes in STI in the individual patient.

It has been shown that externally determined STI quite reliably reproduces internally determined STI (Weissler *et al.*, 1963; Martin *et al.*, 1971). One factor limiting usefulness of STI, however, is that they are quite sensitive to pharmacological interventions and spontaneous left ventricular function changes such as in an anginal attack and with use of digitalis (Pouget *et al.*, 1971; Weissler and Garrard, 1971). We can minimize pharmacological intervention as a cause of the changes in mean STI values in the surgical group. Antiarrhythmics were used only in an insignificant proportion, and the number of patients on propranolol and digitalis in each group did slightly change. However, the significant changes in STI from period 1 to period 2 in the surgical group and the significant difference between the surgical and medical groups were not those expected from changes in drugs alone. Medicines complicate this analysis, but are an important aspect of management. Thus, patients were not excluded because they were on drug therapy.

Objective post-surgical evaluation has been made by other groups using cineangiography, evaluation of LV haemodynamics, and exercise studies (Manley *et al.*, 1970; Manley and Johnson, 1972; Bourassa *et al.*, 1972; Anderson, 1972; Chatterjee *et al.*, 1972, 1973; Griffith *et al.*, 1973; Lapin *et al.*, 1973; Alderman *et al.*, 1973; Bartel *et al.*, 1973). Chatterjee *et al.* (1973) showed that two weeks after bypass, coronary artery disease patients with chronic ischaemia had improved wall motion. Manley and Johnson (1972) studied patients before and three months after bypass surgery and showed an improvement in function related to graft patency.

On the other hand, Arbogast, Solignac, and Bourassa (1973) showed no improvement in ejection fraction with patent grafts and a worsening with severely stenosed grafts one year after surgery. Hammermeister *et al.* (1974) showed no significant changes in LV volume measurements in the group as a whole or in the subgroup with patent grafts 1-to 14 months after surgery, despite improvement in symptomatology and exercise performance. In patients studied 2 weeks and 1 year after bypass, Bourassa *et al.* (1972) showed an improvement of left ventricular wall motion in only one-half and an increased abnormality of wall motion in over 40 per cent with inadequate patency, compared with preoperative studies.

As for the STI changes after bypass, Johnson *et al.* (1972), in a study of 11 patients 3 months after bypass, showed a decreased PEPI, increased LVETI, and decreased PEP/LVET compared with preoperative studies, similar to our results.

In conclusion, serial STI showed improvement in PEPI, LVETI, and PEP/LVET in a group of surgical patients in the 3- to 6-month period after bypass surgery. This improvement was found neither in patients with coronary artery disease not subjected to surgery nor in patients with anginal symptoms with less than significant coronary artery obstruction. This suggests an improvement of function, and the high follow-up rate of patient re-evaluation suggests that serial STI may be valuable as a large-scale determinant of LV per formance after surgery.

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# His bundle recordings in diagnosis of impulse formation in Kent and Mahaim tracts

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*His bundle electrograms were recorded in 2 patients with ectopic beats arising in accessory atrioventricular tracts. Case 1 had Wolff-Parkinson-White (WPW) type A and a left-sided Kent tract with a short effective refractory period. Though ectopic impulse formation most probably occurred within the Kent tract itself, a vulnerability-related origin in the ventricular muscle close to the distal end of the Kent tract could not be excluded. In Case 2, with a Mahaim tract extending from His bundle to ventricles, there were three types of QRS morphologies resulting from: (a) atrioventricular conduction exclusively through the normal pathway; (b) atrioventricular conduction through both, normal pathway, and Mahaim tract; and (c) ectopic impulse formation in the Mahaim tract. Specialized electrophysiological studies were essential to diagnose these unusual arrhythmias.*

There have been several reports postulating ectopic impulse formation in accessory atrioventricular tracts (Bix, 1953; Katz and Pick, 1956; Soffer, 1962; Scherf and Cohen, 1964; Bermudez and Childers, 1970; Mustakallio and Sarkkonen, 1973; James and Puech, 1974; Wyndham and Rosen, 1976). However, this assumption could not be proven because His bundle recordings were not obtained in these cases. This justifies the presentation of two possible examples of ectopic impulse formation within Kent and Mahaim tracts.

## Subjects and methods

His bundle recordings were obtained in 2 patients referred for electrophysiological studies after the procedure had been explained and consent obtained (Castillo and Castellanos, 1970; Castellanos *et al.*, 1973b). For the purpose of the presentation a Kent tract was considered as an accessory atrioventricular connexion not attached to this normal AV node-His Purkinje system. A Mahaim tract was a His-ventricular connexion.

The AH interval was measured from onset of atrial (A) to onset of His bundle (H) deflections in the His bundle electrographic (HBE) leads. The HV interval was measured from the onset of the H deflection to the beginning of ventricular depolarization in whichever lead (intracardiac or surface) it occurred first.

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## Case 1

Additional information from this patient with Wolff-Parkinson-White (WPW) type A, including the morphology of sinus and driven beats, the functional properties of the Kent tract, and the mechanisms of repetitive arrhythmias has been presented elsewhere (Castellanos *et al.*, 1973b).

Sinus impulses were conducted exclusively through the AV node-His Purkinje system with a complete right bundle-branch block morphology (first two beats in Fig. 1 and first beat in Fig. 2). The AH and HV intervals measured 85 and 55 ms, respectively. Premature atrial impulses (third beat in Fig. 1 and second beat in Fig. 2) were conducted to the ventricles almost exclusively through the Kent tract with WPW type A morphology. The PR interval became shorter and the H deflection appeared at, or slightly after, the onset of a wide QRS complex which occurred before the end of the antecedent T wave.

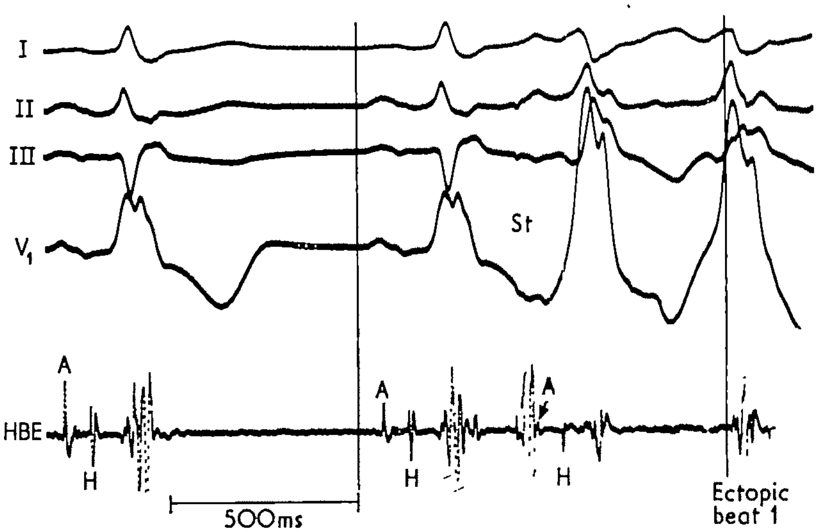

FIG. 1 *(Case 1) Intermittent WPW syndrome type A (third QRS complex) with an ectopic beat (1) probably arising in a left side Kent tract. A=low right atrial electrogram. HBE=His (H) bundle electrographic lead. St=pacemaker stimulus artifact.*

In addition, Fig. 1 shows an ectopic (last) QRS complex almost identical to the previous (third) ventricular complex which in this patient represented exclusive Kent conduction. This ectopic beat (1) was not preceded by a P wave nor an H deflection. Though it most probably arose in the Kent tract itself a 'true' ventricular extrasystole originating close to the lower end of the tract could not be excluded completely.

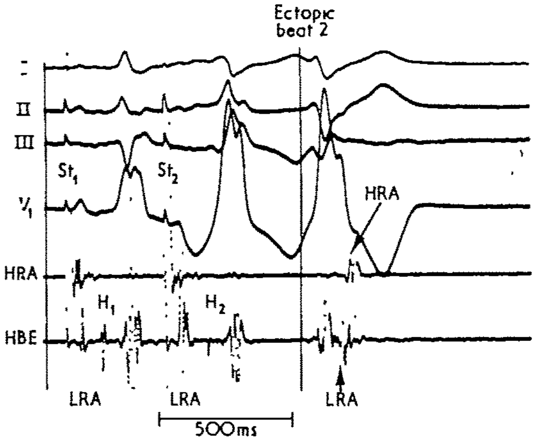

FIG. 2 *(Case 1) Ectopic beat (2) arising in a left-sided Kent tract or in the ordinary ventricular muscle close to its distal end.*

In contrast, the last QRS complex in Fig. 2 was not identical to that resulting from exclusive accessory AV pathway conduction (second ventricular complex) because: (a) the QRS axis changed to a closer to ±180° position; (b) lead II became predominantly negative; and (c) in V1 the height of the R wave increased with the notch being displaced downward. This ectopic beat (2), which was followed by a P wave with a low-to-high right atrium sequence, could have arisen in: (a) the ventricular muscle (close to the end of the Kent tract) or (b) within the latter itself, the different contour being the result of irregular propagation through incompletely recovered muscle. The latter possibility was supported by its coupling interval (360 ms) which was shorter than that of the ectopic beat in Fig. 1 (400 ms), both being preceded by similar RR (or VV) intervals.

To summarize, in this patient impulse formation probably occurred in a left-sided Kent tract. Yet, vulnerability-related ventricular ectopic beats could not be completely excluded.

## Case 2

Other tracings from this 23-year-old man with intermittent conduction through a Mahaim tract have been discussed previously (Castillo and Castellanos, 1970). However, the duration of the pertinent intervals in Fig. 3–5 was determined as currently performed in our department. This re-

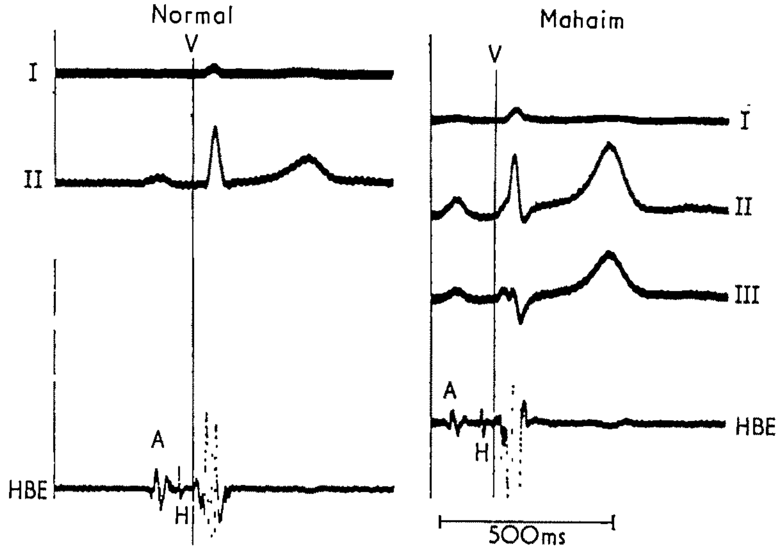

FIG. 3 *(Case 2) Sinus rhythm with exclusive conduction through the normal atrioventricular pathway (left) and through both normal atrioventricular pathway and Mahaim tract extending from His bundle to ventricles (right).*

sulted in slightly different values from those previously reported (Castillo and Castellanos, 1970).

During sinus rhythm with exclusive conduction through the AV node-His Purkinje system the PR, AH, HV intervals and QRS complexes measured 140, 85, 45 and 80 ms, respectively (Fig. 3, left). In contrast, sinus beats propagating through both normal atrioventricular pathway and Mahaim tract had PR, AH, and HV intervals measuring 130, 85 and 35 ms, respectively (Fig. 3, right). In this beat the HV interval represented conduction time from His bundle to ventricles through the Mahaim tract. The QRS complex showed an initial slurring (delta wave) and a duration of 90 ms.

During atrial stimulation the AH interval increased while the HV interval and QRS complex remained unchanged (Fig. 4). This response to atrial pacing excluded Kent conduction and it is in keeping with a functional electrophysiological Mahaim tract extending from His bundle to ventricles (Castillo and Castellanos, 1970).

An escape rhythm also occurred intermittently in this patient (Fig. 5). Though the QRS complexes were wider (130 ms) and the HV intervals shorter (15 to 20 ms) than those of sinus beats conducted through both normal pathway and Mahaim tract (Fig. 3, right), the direction of the initial slurring (delta wave) was the same.

These ectopic beats probably did not originate in the His bundle with conduction to the ventricles via both His-Purkinje and Mahaim pathways, since the HV interval and QRS morphology would have been similar to those in Fig. 3, right. Neither did they arise in the proximal bundle-branches or fascicles, since, in absence of bundle-branch disease (Fig. 3, left), the QRS complexes should have shown an 'incomplete' (not a 'complete' as in Fig. 5) bundle-branch block pattern with an H deflection appearing *after* the onset of ventricular depolariza-

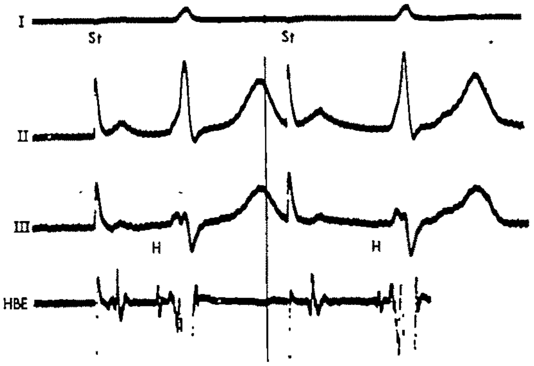

FIG. 4 *(Case 2) Atrial stimulation showing (by comparison with Fig. 3, right) an increase in AH interval without any change in HV interval or QRS morphology.*

tion (Rosenbaum *et al.*, 1970; Castellanos *et al.*, 1972).

The possibility that the deflection in Fig. 5 was a right bundle electrogram preceded by the 'missed' (the result of technical reasons) H deflection of a His bundle escape rhythm cannot be excluded completely. However, for this to occur the His bundle beats must have had bradycardia-dependent (phase 4) bundle-branch block, which appears unlikely in a young individual without heart disease (proven by cardiac catheterization) who electrophysiologically and clinically had pre-excitation syndrome and was taking no medicines.

In summary, this patient had an escape rhythm possibly arising within a Mahaim tract extending from His bundle to ventricles.

## Discussion

Although several authors have suggested that impulse formation could occur within the accessory atrioventricular tracts themselves (Bix, 1953; Katz and Pick, 1956; Soffer, 1962; Scherf and Cohen, 1964; Bermudez and Childers, 1970; Mustakallio and Saikonnen, 1973; James and Puech, 1974; Wyndham and Rosen, 1976), as far as we know this is the third report in which specialized intracardiac recordings have been used to support the validity of the assumptions (Coumel *et al.*, 1973).

Puech and Grolleau (1972) discussed the tracings of a patient with WPW type B who also had late extrasystoles interpreted as originating in a low atrial focus. The latter, however, could have arisen in the Kent tract, the corresponding P wave (which preceded the wide QRS complex) resulting from simultaneous depolarization of the atria by both sinus and ectopic wavefronts.

The differential diagnosis between impulse formation in Kent and Mahaim tracts is difficult to make from the surface electrocardiogram alone. Identification of the ectopic beats requires prior knowledge of the type(s) of pre-excitation present. Since this cannot always be done from the analysis of surface leads only, specialized intracardiac studies are essential (Castillo and Castellanos, 1970).

For example, in patients with Kent tracts, atrial stimulation from the appropriate sites and cycle lengths will eventually show that the His bundle deflection appears after the onset of ventricular depolarization (Castillo and Castellanos, 1970). If an ectopic beat has a QRS morphology identical to that resulting from exclusive Kent conduction (Fig. 1) impulse formation in the latter can indeed be postulated. However, extrasystoles arising in the ventricular muscle close to the lower end of the tract will show a similar morphology. Our first patient had a Kent tract with a short effective refractory period (Castellanos *et al.*, 1973b). Therefore, premature atrial impulses were able to reach the ventricles early enough to produce a QRS complex appearing on top of the preceding T wave (vulnerable period). For this reason repetitive firing in the ventricular muscle close to the end of the Kent tract could have been the mechanism of the ectopic beats in Fig. 1 and 2.

On the other hand, a *very premature* impulse arising in the Kent tract could propagate very irregularly throughout the ventricles because of relative refractoriness (Castellanos *et al.*, 1973a), thus resulting in a QRS morphology (Fig. 2) different from that of beats arising later in the cycle (Fig. 1).

There have been few reports (using His bundle recordings) describing the features of supraventricular beats conducted to the ventricles simultaneously through the AV node-His-Purkinje system and a Mahaim tract extending from His bundle to ventricles (Castillo and Castellanos, 1970). This was postulated in Case 2 by the alternation of narrow and wide QRS complexes during sinus rhythm (Fig. 3) and by assessment of the effects of atrial stimulation on QRS duration and HV intervals (Fig. 4). It should be stressed that we are not referring to those cases in which an electrophysiological AV nodal bypass has coexisted with a Mahaim tract (Coumel *et al.*, 1972; Castellanos *et al.*, 1975), neither to the cases in which the latter has extended from the AV node to ventricles (Tonkin *et al.*, 1975) or bundle-branches to ventricles (Castellanos *et al.*, 1975).

Coumel *et al.* (1973) reported a case in which there was a Kent tract (or a Mahaim tract associated with a James tract) coexisting with complete AV block resulting from 'congenital absence of the bundle of His'. Because of the latter an H deflection was not recorded in this patient. Escape beats were occasionally seen, but it could not be determined whether they arose in a Mahaim or in a Kent tract.

The Mahaim escapes depicted in Fig. 5 were not preceded by P waves. That the impulses reached the ventricles exclusively through the accessory tract was suggested by the similarities of the initial portions of the QRS complexes (delta wave) of fusion and escape beats, as well as by the increase in total ventricular activation time and decrease in H-V intervals in the latter (Fig. 5) as compared with the former (Fig. 3, right).

It should be stressed that in Fig. 5, the H-V interval did not represent linear conduction time from His bundle to ventricles through the Mahaim tract but differences in arrival of excitation at these

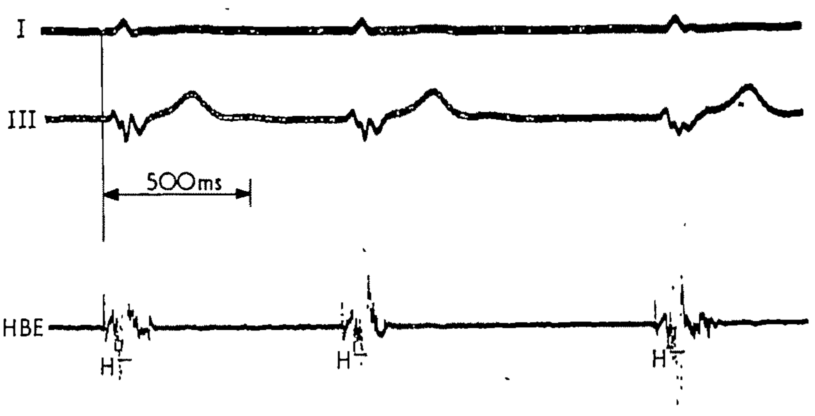

FIG. 5 *(Case 2) Mahaim escapes showing (in reference to Fig. 3, right) shorter H-V intervals and wider QRS complexes. The ventricles were depolarized exclusively through the Mahaim tract. $H^-$ indicates retrograde activation of His bundle from the site of origin (see Fig. 6, left)*

sites. Thus in Fig. 5 the His bundle was activated regrogradely from the Mahaim tract whereas in Fig. 3, right, and in Fig. 4 it was depolarized antegradely from the atrioventricular node.

The differential diagnosis of the type of Mahaim escapes postulated in this communication includes impulse formation in: (a) His bundle (atrioventricular junction) with conduction to the ventricles via both His-Purkinje system and Mahaim tract (Pick, 1956); (b) His bundle (atrioventricular junction) with conduction exclusively via the Mahaim tract (Pick, 1956); and (c) bundle-branches, or fascicles of the left bundle-branch (Rosenbaum *et al.*, 1970) (Fig. 6).

The electrophysiological evaluation of pre-excitation syndromes with multiple catheter electrodes (which are needed in most patients with reciprocating atrioventricular tachycardias) requires a thorough understanding of iatrogenic factors which can lead to errors in interpretation. For example, mechanical stimulation of the ordinary muscle at the right ventricular inflow tract by the catheter electrode recording His bundle activity can stimulate impulse formation in a right septal Kent tract (WPW type B). Likewise, mechanical stimulation by a catheter introduced in the distal coronary sinus or great cardiac vein produces pseudo (left-sided) Kent extrasystoles in patients with WPW type A (Castellanos *et al.*, 1973c). In these beats the corresponding QRS morphologies are different from those resulting from exclusive Kent conduction. Moreover, the onset of the ven-

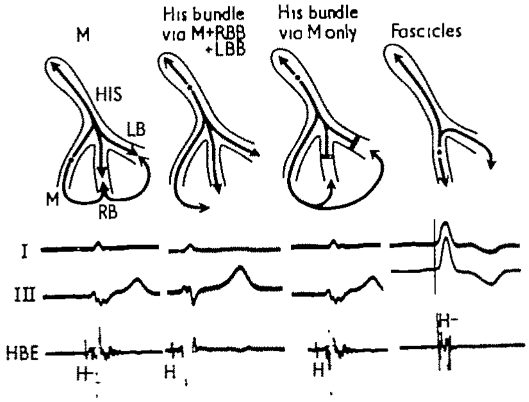

FIG. 6 *(Case 3) Differential diagnosis of Mahaim (M) escapes (left-sided schematic). H-V intervals and QRS morphologies are similar to those of beats shown in Fig. 5. Impulse formation in His bundle with conduction through both normal atrioventricular pathway and Mahaim tract (second schematic) results in HV intervals and QRS morphologies similar to those of beats in Fig. 3, right. Impulse formation in His bundle with conduction exclusively through Mahaim tract (third schematic) results in HV intervals as in Fig. 3, right, and QRS morphologies as in Fig. 5. Fascicular beats (last schematic) have short H-V or ($VH^-$) intervals with QRS morphologies depending on the site or origin: right bundle-branch (RBB), left bundle-branch (LBB) or fascicles of the left bundle-branch.*

tricular electrogram recorded by the corresponding catheter electrodes can occur as early as 20 ms before the onset of QRS in the surface leads (Castellanos *et al.*, 1973c).

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# Frequency of arrhythmias and other cardiac abnormalities in fulminant hepatic failure

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*In a series of 106 patients with fulminant hepatic failure and grade 4 encephalopathy, cardiac arrhythmias and other abnormalities occurred in 92 per cent. The most common was sinus tachycardia (75%) and this was the only abnormality in 22 per cent of the patients. Sudden cardiac arrest occurred in 25 per cent, various ectopic beats in 20 per cent, and heart block or bradycardia in 18 per cent. Other electrocardiographic abnormalities, mostly of the T wave and ST segment, were found in 31 per cent. Cardiac and respiratory arrests were usually unrelated to each other and both frequently occurred without warning. Only 7 out of 71 patients with arrhythmias other than sinus tachycardia survived, compared with 15 out of 31 patients without them ($P<0{\cdot}005$). During the latter part of the series when an arrhythmia computer was used to monitor 38 patients, it was shown that significantly lower arterial oxygen levels occurred in those with arrhythmias, other than sinus tachycardia, than in those without. They were also found to be more acidotic and hyperkalaemic, and a higher number required dialysis and ventilation. Macroscopical cardiac abnormalities including scattered petechial haemorrhages, small pericardial effusions, and fatty, pale, and flabby ventricles, were found at necropsy in 64 per cent of the patients examined. Combinations of these macroscopical abnormalities occurred, particularly in the paracetamol overdose group. Another necropsy finding of possible significance in the pathogenesis of arrhythmias was cerebral oedema, present in 48 per cent of the patients examined, and often associated with coning of the brain stem. However, 7 of the 16 patients who suffered asystolic cardiac arrests had no macroscopical abnormality of either heart or brain.*

*In the management of patients with fulminant hepatic failure continuous cardiac monitoring is essential. Correction of the biochemical and coagulation defects may decrease the frequency of arrhythmias but studies of the mechanism and control of cerebral oedema and its relation to cardiovascular function are urgently needed.*

Fulminant hepatic failure impairs the function of many organs other than the liver. In the cardiovascular system, various changes including peripheral vasodilatation, tachycardia, high cardiac output, and hypotension have been described (Trey and Davidson, 1970; Williams, 1974). They have been little studied, though experimental interest in the effects of bile on the cardiovascular system dates from the turn of the century (Meltzer and Salant, 1905; Bunting and Brown, 1911; Emerson, 1929; Wakim, Essex, and Mann, 1940). Abnormalities of the T wave in the electrocardiogram of patients with infectious hepatitis, all of whom survived, were described by Dehn, Feil, and Rinderknecht (1946) and in 4 patients who died from viral hepatitis histological changes suggesting myocarditis were found by Saphir, Amromin, and Yokoo (1956). Bell (1971) drew attention to widespread petechial haemorrhages, infiltrations of lymphocytes, fatty degeneration, flabby dilated ventricles, and oedema of the subendocardial tissue found at necropsy in patients dying of viral hepatitis. Many of these patients had suffered cardiac arrhythmias during their illness.

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Apart from direct myocardial involvement by hepatitis A and B viruses, many of the biochemical abnormalities, as well as changes in brain-stem function, present in fulminant hepatic failure could be important in the pathogenesis of these arrhythmias. These factors are considered in this study and an analysis is made of the frequency and types of arrhythmia occurring in 106 patients with fulminant hepatic failure. In the latter part of the series, a cardiac arrhythmia computer was used to try to identify specific patterns or sequences of arrhythmias to help understand their development and prevention.

## Patients and methods

The 106 patients were admitted to the Liver Unit, King's College Hospital, during the period October 1969 to October 1974. All of them deteriorated to grade 4 encephalopathy (as defined by Trey and Davidson, 1970) during the course of their illness. The liver failure was most commonly caused by hepatitis A or B or by overdoses of paracetamol taken in suicidal attempts (Table 1).

The patients all received standard supportive therapy with intensive nursing care and 24-hour medical cover, and over the latter 12 months of the study were looked after in a purpose-designed, two-bedded liver failure unit. Of the earlier patients, 6 were treated with exchange transfusion, 4 with extracorporeal liver perfusion, and 1 was cross-circulated with a human volunteer. In the 34 cases investigated since October 1973, a new technique of temporary liver support based on charcoal haemoperfusion was used (Gazzard *et al.*, 1974). Serum electrolyte estimations, blood gas analysis, liver function tests, and coagulation studies were carried out daily in all patients, or more frequently if indicated.

Necropsies were carried out in 76 of the 84 patients who did not recover. Particular attention was paid to the presence of macroscopical cardiac abnormalities, and in 24 patients sections of the left ventricle were stained for microscopy (16 with haematoxylin and eosin and 8 with Oil Red O). The brain was also routinely examined for cerebral oedema and evidence of coning.

Information on arrhythmias in the first 68 patients was obtained retrospectively from notes, electrocardiograms, and rhythm strips where possible. In 38 of the more recent cases continuous cardiac monitoring was carried out with equipment supplied by Messrs Simonsen and Weel which comprised an arrhythmia recorder, single channel recorder, computer, memory twinscope, and servograph pen drive for arrhythmia write-out. When a steady trace had been produced, three consecutive complexes were compared with respect to the RR interval, QRS width, and QRST area. If any of these differed by ±20 per cent or more of the value stored in the memory, it was registered on the recording system which presented arrhythmias in the form of a histogram.

TABLE 1 *Aetiology of fulminant hepatic failure in 106 patients together with mortality*

| *Aetiology* | *No. of cases* | *% Mortality* |
|---|---|---|
| Virus hepatitis | | |
| Type A | 19 | 73 |
| Type B | 16 | 81 |
| Unclassified | 9 | 100 |
| Paracetamol overdose | 43 | 77 |
| Halothane associated | 12 | 92 |
| Other (drug reactions, etc.) | 7 | 43 |
| Total | 106 | 79 |

*Note:* In virus hepatitis type B, HBsAg was detected by immunodiffusion or radioimmunoassay. In the unclassified cases sera had not been tested.

## Results

Only 9 of the 106 patients had no record of an arrhythmia while in grade 4 encephalopathy. Sinus tachycardia (greater than 100 beats a minute) was the commonest of the arrhythmias, being present in 79 per cent of the patients. It was the only abnormality in 24 per cent. It often occurred before deep coma, and in many instances persisted throughout the illness. Cardiac arrest took place in 27 per cent of the patients. These were asystolic in 16 patients with the remainder caused by ventricular fibrillation or an unspecified cause (retrospective survey). Eleven patients suffered from atrial fibrillation and 8 from supraventricular tachycardia. Ventricular ectopics occurred in 8 patients and atrial or nodal ectopics in 6. Four had more than one type of ectopic, and in another 3 the nature of the ectopic beat was not specified. Ventricular tachycardia was observed in 5 patients and an idioventricular rhythm in 1. Sinus bradycardia was observed in 5 patients and bradycardia of an unspecified nature in another 9. Complete heart block was seen in 2 patients and 2 other patients had first or second degree heart block. Abnormalities of the ST segment and T wave in the electrocardiogram were frequently seen but did not appear to relate to any specific arrhythmia. It was not possible to correlate either the type or frequency of arrhythmia with the aetiology of the fulminant hepatic failure.

Usually the arrhythmias were of relatively short duration and lasted for only a few hours at the most. They either reverted spontaneously or responded

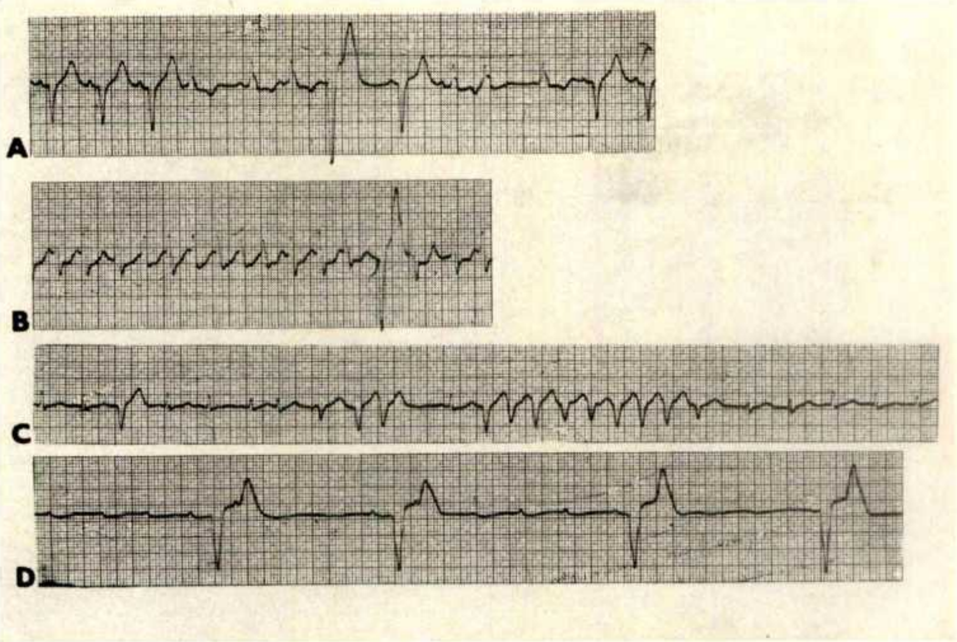

FIG. 1 *Rhythm strips obtained from a 69-year-old man while in grade 4 coma from fulminant hepatic failure caused by a presumed type A hepatitis: (A) Sinus rhythm, intermittent bundle-branch block, and ventricular ectopics; (B) atrial fibrillation which reverted to sinus rhythm with direct current version; (C) episode of ventricular tachycardia; (D) complete heart block. At necropsy the myocardium appeared normal though there were numerous petechial haemorrhages in the pericardium. There was no evidence of brain-stem coning.*

to standard measures (for example, digoxin for supraventricular tachycardia which occurred in 10 patients, atropine for bradycardia, direct current shock for ventricular tachycardia). In addition to the 24 per cent who had sinus tachycardia alone another 6 patients had single types of arrhythmia only (2 had asystolic cardiac arrests and one each with complete heart block, Wenckebach phenomenon, paroxysmal ventricular tachycardia, and supraventricular tachycardia). Another 2 had T wave abnormalities alone. The remaining 65 patients had more than one type of arrhythmia and many had several (Fig. 1), but apart from usually being preceded by a sinus tachycardia, there was no specific pattern in their evolution. Their occurrence was not related to the duration of coma and one patient with a paracetamol overdose sustained an asystolic cardiac arrest while still rousable. Though some of the older patients were troubled by more persistent arrhythmias, their frequency did not appear to increase with age. Thus, the average age of the 11 patients who had periods of atrial fibrillation (an arrhythmia whose incidence might be expected to increase with age) was 34·2 (range 18 to 69) years, as compared with 35·4 (range 10–78) years in those without atrial fibrillation. The appearance of arrhythmias was clearly a poor prognostic sign, as 64 of the 71 patients in whom they occurred (excluding sinus tachycardia) died, compared with only 15 out of 33 without.

Cardiac arrests were frequently asystolic and resuscitation was temporarily successful in 5 instances. However, one patient in whom the liver failure had followed a massive dose of paracetamol, suffered two asystolic arrests while deeply unconscious but eventually survived. Frequently the arrests occurred without warning, though 2 of the 6 that occurred when the cardiac arrhythmia computer was in use were associated with respiratory arrests. In all, 8 of the 38 patients monitored continuously had respiratory arrests and only one of these survived, despite assisted ventilation. Respiratory arrests, like cardiac arrests, were usually preceded by obvious respiratory difficulty comprising tachypnoea, loud coarse crepitations, occasional expectoration of fresh blood, and in-

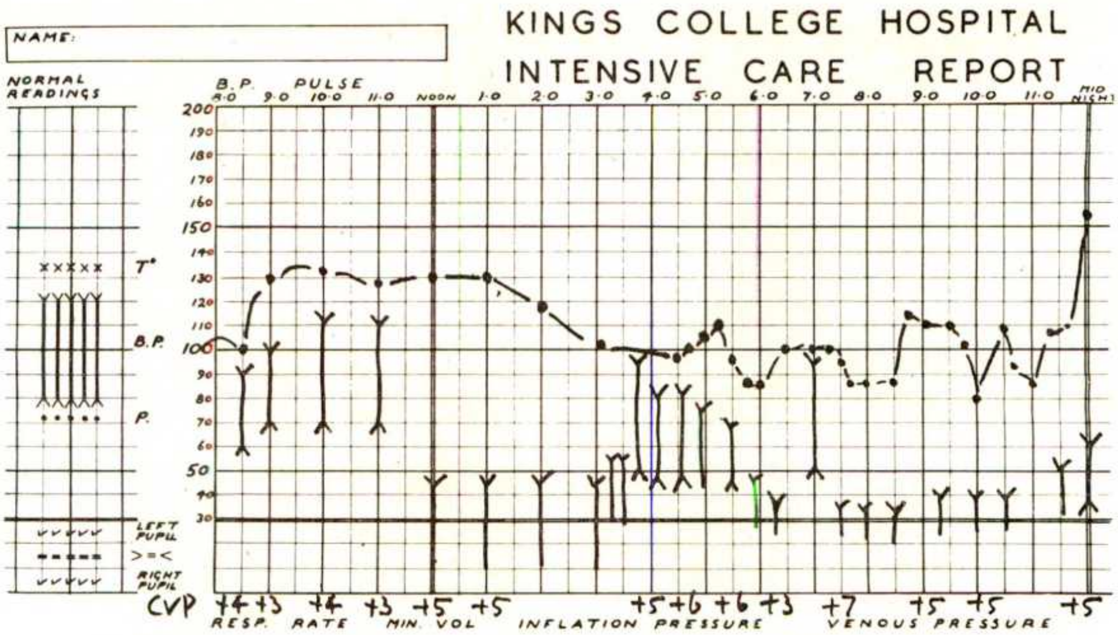

FIG. 2 *Part of nursing chart showing sinus tachycardia and sudden drop of blood pressure with little change of central venous pressure, suggestive of brain-stem coning.*

creasing tachycardia, though sometimes they occurred without warning. Changes of blood pressure, without clinically obvious bleeding or fluid imbalance, which we now consider indicative of brain-stem coning, were sometimes observed immediately before sudden respiratory or cardiac arrests (Fig. 2).

There were no specific arrhythmias associated with charcoal haemoperfusion though a slight fall of blood pressure (10 to 20 mmHg (1·3 to 2·7 kPa)) often occurred within 30 minutes of the start of the procedure. In one patient with a sinus tachycardia, the pulse rate dropped by 10 per cent each time he was perfused and in a 16-year-old patient with a paracetamol overdose, pronounced T wave inversion developed during one perfusion which was reversed by blood transfusion.

## Continuous cardiac monitoring and relevant biochemical changes in 38 patients

Use of the cardiac arrhythmia recording apparatus itself proved satisfactory, but it was often difficult to interpret arrhythmias from the histogram alone because of artefacts arising at the patient-electrode interface. The majority of the arrhythmias recorded by the computer had also been witnessed on the oscilloscope and transcribed on a rhythm strip by the attending physician or nurse. The arrhythmia computer gave a higher recognition rate of supraventricular tachycardia, ectopic beats of all types, atrial fibrillation, and heart block than in the previous 68 patients, though the frequency of sinus tachycardia, serious ventricular arrhythmias, and cardiac arrests remained the same.

The 38 patients were divided into two groups according to the presence or absence of arrhythmias, excluding sinus tachycardia which occurred in all but 4 of them. Differences in the maximum and minimum levels of serum potassium, calcium, phosphate, and arterial hydrogen ion concentration and partial pressure of oxygen in each group (Table 2) were analysed with the Student's t-test• during the period of grade 4 encephalopathy. The only significant differences found were in the mean oxygen levels which were lower ($P < 0·02$) in the patients with arrhythmias. Comparison of the maximum arterial oxygen levels showed that these were higher in the arrhythmia group ($P < 0·05$), and presumably this resulted from the more frequent oxygen enrichment and assisted ventilation requirements of this group. Though the arrhythmia group also had higher hydrogen ion concentrations,

TABLE 2 *Comparison of biochemical and blood gas analysis in 38 patients having continuous cardiac monitoring divided according to presence or absence of arrhythmias other than sinus tachycardia*

| | *Arrhythmias* | |
|---|---|---|
| | *Present (n=25)* | *Absent (n=13)* |
| Arterial hydrogen ion concentration (nmol/l) | 53 ± 6·6—30·2 ± 1·6 | 38·1 ± 2·1—28·5 ± 0·6 |
| Arterial oxygen levels (kPa) | 19·6 ± 1·01—8·44 ± 0·5 | 15·6 ± 1·5—11·12 ± 1·1 |
| Serum potassium levels (mmol/l) | 5·34 ± 0·26—3·27 ± 0·14 | 4·58 ± 0·19—2·97 ± 0·14 |
| Serum calcium (mmol/l) | 2·28 ± 0·04—1·93 ± 0·05 | 2·25 ± 0·06—1·99 ± 0·05 |
| Serum phosphorus (mmol/l) | 1·54 ± 0·18—0·57 ± 0·12 | 1·03 ± 0·13—0·45 ± 0·09 |
| Prothrombin time (seconds prolonged) | 23·3 ± 9·43 | 24·1 ± 3·99 |
| Plasma bilirubin (μmol/l) | 400 ± 39·3 | 411·9 ± 68·18 |
| Survivors | 6 | 10 |
| Numbers requiring | | |
| dialysis | 9 | 3 |
| ventilation | 13 | 2 |

*Note:* The two sets of values shown for each measurement represent mean maxima and minima (± 1 SEM) respectively observed while patients were in grade 4 encephalopathy. Prothrombin times and plasma bilirubin levels were the maximum recorded during this period.

potassium and phosphate levels, the differences were not statistically significant ($P > 0{\cdot}2$, $> 0{\cdot}1$, and $> 0{\cdot}1$, respectively). As indices of liver cell dysfunction, the maximum levels of serum bilirubin and maximum prolongation of the one-stage prothrombin time recorded during the illness were compared, but no significant differences between the two groups of patients were found. The number of patients requiring dialysis and ventilatory support was higher in the group with arrhythmias, but this was probably only a reflection of their more severe illness and poorer prognosis already referred to.

## Cardiac abnormalities and other findings at necropsy

Forty-two of the 76 hearts examined at necropsy were macroscopically abnormal (Fig. 3). In 33 hearts the main changes could be grouped as follows: a pale, flabby, fatty myocardium (11 cases), scattered petechial haemorrhages (15 cases), dilatation of the ventricles without other organic cause (7 cases), and pericardial effusions (11 cases). Ten of these cases showed more than one abnormality (9 with 2 abnormalities and one with 3). Eight of these 10 hearts came from the paracetamol overdose patients but apart from the frequency of multiple abnormalities in this group, no particular associations were found between them. Larger bleeds had occurred in the intraventricular septum in 3 of the hearts with petechial haemorrhages, and in one other case, with a diagnosis of hepatitis A infection, the myocardium was frankly haemorrhagic. Pericardial effusions were seldom more than 50 ml in volume. They were occasionally bloodstained, but none had given rise to cardiac tamponade. Of the

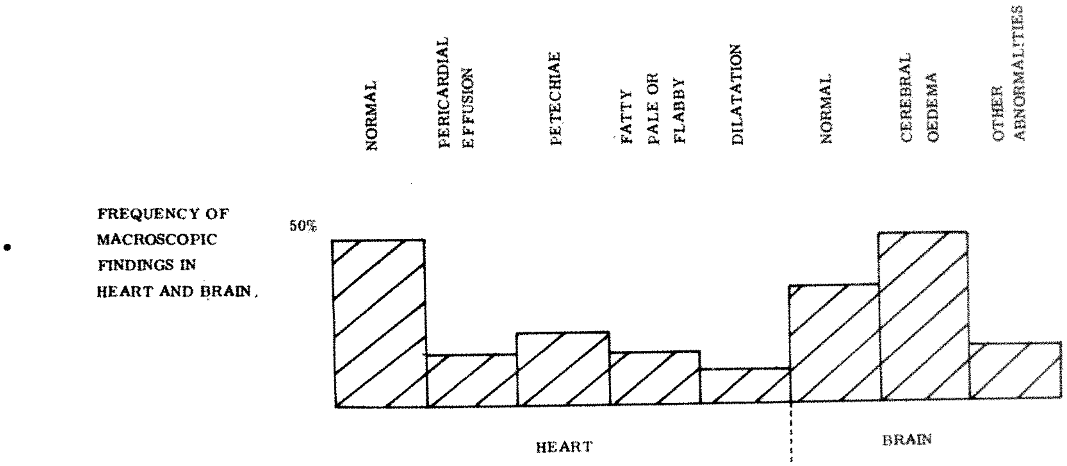

FIG. 3 *Frequency of macroscopical cardiac and cerebral abnormalities at necropsy in patients dying from fulminant hepatic failure, presented in form of histograms.*

11 patients with fatty, pale, flabby hearts, 9 came from the paracetamol overdose group.

In the remaining 9 of the 42 hearts showing abnormalities, changes unrelated to hepatic failure were found. Three of these had left ventricular hypertrophy caused by longstanding hypertension and there were single cases of right ventricular hypertrophy caused by emphysema, aortic regurgitation resulting from Marfan's syndrome, a Starr valve prosthesis, and infiltration of the myocardium with excess adipose tissue. Diffuse myocardial abscesses and subacute bacterial endocarditis which had not been detected during life were found in the final two cases. They may have contracted infection as a complication of their fulminant hepatic failure.

No correlation could be detected between macroscopical abnormalities of the heart and the type of arrhythmia that had occurred during life. Indeed 3 of those with macroscopical abnormalities had no arrhythmias, 5 had had asystolic cardiac arrests, and the remaining 34 all had arrhythmias of one sort or another. On the other hand, 10 of the 34 patients with macroscopically normal hearts had cardiac arrests and the other 24 all had arrhythmias.

Paraffin sections of the left ventricle taken from 16 of the 33 patients who died from a paracetamol overdose were stained with haematoxylin and eosin and examined microscopically. Evidence of finely divided intracellular fat was found in 12 of them, irrespective of whether macroscopical changes had shown a fatty appearance. Specific staining for fat with Oil Red O in another 5 showed fine intracellular droplets of fat in all of them (Fig. 4). In addition, intracellular fat was also shown with this stain in sections of the left ventricle in 2 of 3 patients who died from fulminant hepatic failure caused by viral hepatitis. In 4 cases who died from causes other than liver disease, no fat was seen with Oil Red O.

### Cerebral changes

Of the 72 patients whose brains were examined at necropsy, cerebral oedema was present in 34, with structural changes caused by coning in 12. Three of these 12 patients had suffered asystolic cardiac arrests, as had 4 others with cerebral oedema, but no coning. However, in the 9 other cases who had asystolic cardiac arrests, the brain was normal in 6. The remaining 3 were not examined. Cerebral oedema was found in 7 of the brains examined from the 8 patients suffering respiratory arrests, with coning in 5.

## Discussion

The frequency of arrhythmias in this series was as high as 92 per cent, if sinus tachycardia is included. If the patients in whom sinus tachycardia was the only abnormality are excluded, 70 per cent had arrhythmias or other electrocardiographic abnormalities. Though a sinus tachycardia is a common finding in sick patients, the rise in pulse rate often occurred before clouding of consciousness. This clinical sign must be included together with the leucocytosis and severe prolongation of prothrombin time that may herald a fulminant course in an acute hepatitis (Ritt *et al.*, 1969). After reviewing reports of electrocardiographic abnormalities in patients with infectious hepatitis, and from his own experience with 8 patients, Lyon (1947) concluded that the virus might directly involve the heart. However, the cardiac histology cited as evidence for this had been studied only at necropsy, and though the changes could have resulted from virus myocarditis they may possibly also have been the result of the accumulation of bilirubin, bile acids, and other potentially toxic metabolites that are inevitably retained in these cases. The diffuse fatty infiltration of the myocardial cells, which had been reported previously in patients who died from virus hepatitis, was, in our series, also found in those patients with hepatic failure from a paracetamol overdose. Reports have mentioned electrocardiographic abnormalities after paracetamol overdose (MacLean *et al.*, 1968; Will and Tomkins, 1971; Kerr, 1973) and histological changes in the myocardium (Pimstone and Uys, 1968; Sanerkin, 1971). In one patient in this series a 12-lead electrocardiogram taken a few hours after an overdose of paracetamol (Fig. 5) when the serum level of the drug was 49 µg/ml showed right axis deviation and inferolateral ST and T wave changes. She developed hepatic coma and died 5 days later from an asystolic cardiac arrest. Necropsy showed mild left ventricular hypertophy, scattered petechial haemorrhages on pericardium and endocardium, and minimal atheroma of the coronary arteries. The brain was slightly swollen and congested.

To study further the possible cardiotoxic effects of this drug, we performed 12-lead electrocardiograms and serum cardiac isoenzyme estimations in 10 patients who had ingested sufficient paracetamol to sustain liver damage but who never became encephalopathic (Table 3). However, only one patient had a rise in serum creatinine phosphokinase and his electrocardiogram suggested pericarditis. In three others the T waves were flattened and inverted. It is not clear whether the electrocardiographic abnormalities differed significantly from those reported by Dehn *et al.* (1946) in noncomatose cases of infectious hepatitis. Certainly many electrocardiographic abnormalities occurred

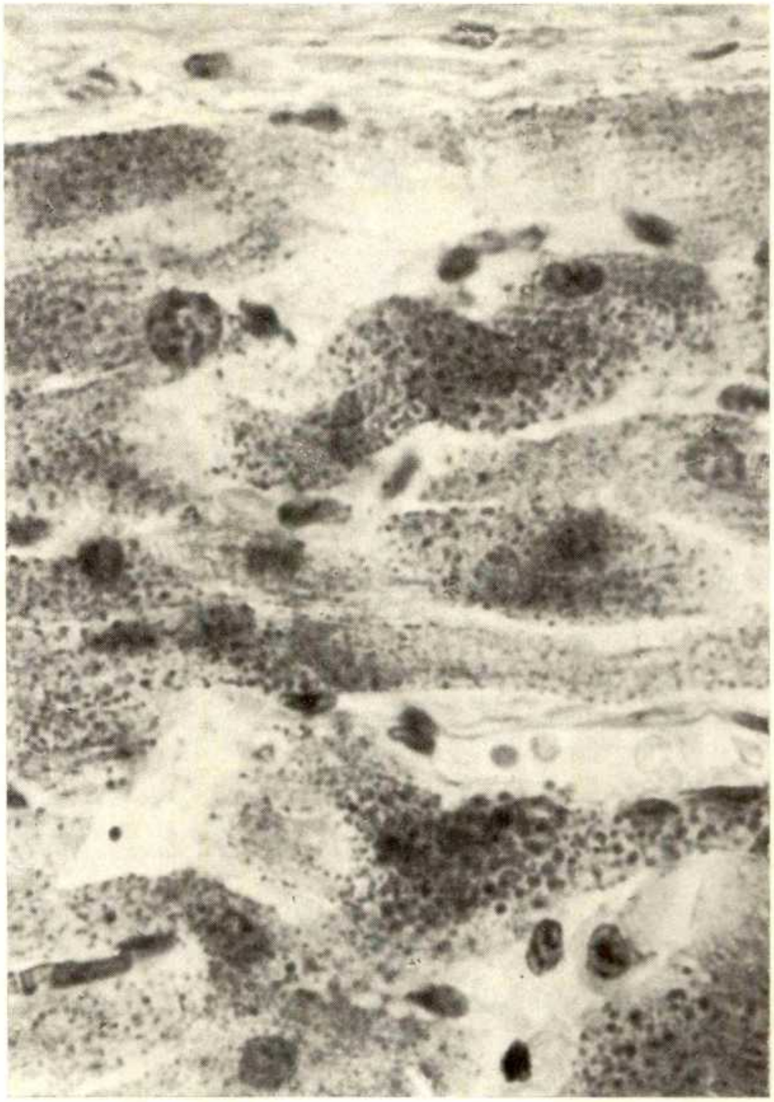

FIG. 4 *Photomicrograph of myocardium from a patient who died after an overdose of paracetamol, showing tiny (dark) lipid droplets in the sarcoplasm. These changes were usually most prominent in the subendocardial region. Cryostat section (Oil Red O × 1600).*

in comatose patients with fulminant hepatic failure from causes other than excess paracetamol ingestion, and included widespread T wave inversion or ST-T segment depression, and peaked T waves and persistent U waves when serum potassium levels were normal. The fact that multiple macroscopical abnormalities of the heart occurred more commonly in the paracetamol group may merely reflect the extremely rapid course of the liver failure in these patients.

The thrombocytopenia and hypoalbuminaemia that develop in the later stages of fulminant hepatic failure almost certainly contribute to the development of petechial haemorrhages and pericardial effusions, respectively. Many biochemical abnormalities are known to have adverse effects on myocardial function and conduction, a subject that has been reviewed in detail by Surawicz (1967). Those found in hepatic failure concern variations beyond physiological limits of serum potassium,

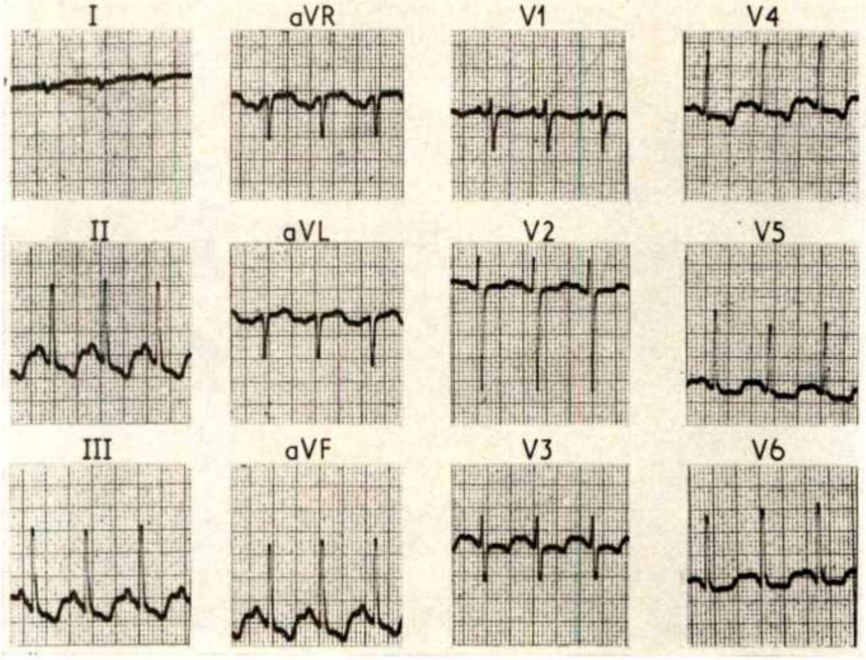

FIG. 5 *12-lead electrocardiogram from a patient a few hours after a paracetamol overdose which showed right axis deviation and inferolateral ST and T wave changes. At necropsy there was mild left ventricular hypertrophy with scattered petechial haemorrhages on the endocardium and pericardium with only minimal atheroma of the coronary arteries. The brain was slightly swollen, and the lungs normal.*

TABLE 3 *Indices of cardiac and liver dysfunction in 10 patients who had ingested paracetamol in suicide attempts but in whom hepatic damage was not severe enough to lead to encephalopathy*

| *Case No.* | *Sex* | *Age (y)* | *Amount of paracetamol ingested (g)* | *Electrocardiogram* | *Maximum abnormality of:* | | |
|---|---|---|---|---|---|---|---|
| | | | | | *Serum creatinine phosphokinase (i.u./l)* | *Serum bilirubin (µmol/l)* | *Prothrombin time (seconds prolonged)* |
| 1 | F | 23 | ? | Normal | Normal | 615·2 | 38 |
| 2 | F | 33 | 25 | Inverted T waves in lead 3 | — | 143·6 | 49 |
| 3 | M | 24 | 50 | Sinus bradycardia ST elevation V 5–6 and inferior leads | 600 | 76·9 | 30 |
| 4 | M | 46 | 40 | Normal | — | 138·4 | 19 |
| 5 | F | 19 | 25 | Flat T waves leads 3, aVF, V2 | Normal | 170·9 | 33 |
| 6 | M | 38 | ? | — | Normal | 76·9 | 12 |
| 7 | F | 52 | 25 | Normal | Normal | 37·6 | 15 |
| 8 | F | 23 | 45 | Flat T waves | Normal | 99·1 | 30 |
| 9 | M | 39 | 25 | Normal | Normal | 188·0 | 18 |
| 10 | M | 52 | ? | Sinus tachycardia | Normal | 73·5 | 17 |

calcium, and magnesium, which all adversely affect contractility, excitability, and the conducting system. Szekeres and Papp (1967) showed that hypoxia increased the susceptibility of the heart to arrhythmias and that this is mediated by the central nervous system. Alkalosis, when induced experimentally in animals, reduces myocardial contractility and ventricular function (Cook, Webb, and Unal, 1965). The correction of cardiac arrhythmias in patients with myocardial infarction who may be suffering from a respiratory alkalosis and hypokalaemia, in addition to hypoxia, can be difficult if these abnormalities are not attended to first (Ayres and Grace, 1969). Alkalosis, comprising both a respiratory factor and hypokalaemia, is prominent early in the course of fulminant hepatic failure and before the onset of renal failure, and may require intravenous potassium supplements. Artificial ventilation sometimes provides an opportunity to correct the respiratory element, and haemodialysis the metabolic component (by lowering the *p*H of the dialysis bath). The short duration of many of the arrhythmias in our patients may account for the difficulty in implicating any one factor on specific occasions. This is why we chose to compare the maximum variations of a number of biochemical parameters during the period of grade 4 coma. The only significant differences found, namely in the arterial oxygen tensions which were both lower and higher in the group with arrhythmias, may be explained by the higher frequency of respiratory insufficiency and ventilatory support needed in this group.

The relation between lipid infiltration of the heart and sudden death has been debated for a number of years. More recently the relation of the raised blood levels of free fatty acids and arrhythmias after myocardial infarction has received clinical and experimental investigation (Kurien and Oliver, 1966; Oliver, Kurien, and Greenwood, 1968). Rowe, Neilson, and Oliver (1975) claimed reduction of the frequency of ventricular tachycardia after myocardial infarction by a nicotinic acid analogue that lowered serum-free fatty acids. Though not measured in the present series, raised serum levels of free fatty acids in fulminant hepatic failure are comparable to those occurring after myocardial infarction (Muto and Takahashi, 1964) and the accompanying hypoalbuminaemia that develops may aggravate their effects (Willebrands, Ter Welle, and Tasseron, 1973).

The influence of rises in intracranial pressure on the cardiovascular and respiratory status of these patients is difficult to assess, but could well be of major importance. Cushing (1902) first described the occurrence of cardiac and respiratory arrests in dogs with experimentally-induced rises of intracranial pressure, effects that were shown to be mediated by the vagus nerve. Moderate rises of intracranial pressure sensitize the heart to the effects of circulating catecholamines (Smith and Ray, 1971) and recently Jachuck *et al.* (1975) have recorded electrocardiographic abnormalities in patients occurring *pari passu* with changes of intracranial pressure. These comprised prominent U waves, ST-T segment changes and notched T waves, and QT interval abnormalities. Many of these changes have been observed in our patients, and monitoring of intracranial pressure may prove worth while in the future.

The cause of cerebral oedema in fulminant hepatic failure, which has been reported by others (Ware, D'Agostino, and Combes, 1971), is unknown. We now suspect coning of the brain-stem in our patients whenever sudden changes of blood pressure and pulse rate occur without obvious explanation. A patient who has been quiet and unresponsive for several hours may become restless and start to groan, his circulatory and respiratory status at the same time becoming unstable. If the patient survives this episode he usually requires ventilatory support, and progressive slowing of the pulse and a drop in body temperature result over the course of several days. Though we presume in such cases that the respiratory arrest is precipitated by the rise of intracranial pressure, it is very likely that the application of ventilatory support will allow the further evolution of cerebral oedema and other changes that would not have occurred had the patient been allowed to die.

The use of the arrhythmia computer increased the rate of recognition of arrhythmias in this investigation and probably alerted clinicians to the correctable biochemical abnormalities such as hypoxia. The occurrence of cardiac arrest and hypotension almost certainly jeopardize liver and brain function further. In cases recovering spontaneously, arrhythmias disappear as the encephalopathy recedes. Though little can be done at the moment to prevent or treat cerebral oedema, or to prevent structural changes in the heart, close supervision of the patient's biochemical and respiratory status may help to avoid arrhythmias and so improve prognosis.

Continuous cardiac monitoring speeds and facilitates the identification of arrhythmias and is a valuable adjunct in their management.

This investigation is part of a programme of research into fulminant hepatic failure, receiving support from the Medical Research Council and the Wates foundation. The cardiac arrhythmia computer and other monitoring equipment was generously supplied by Messrs Simonsen and Weel Ltd. We are indebted to Dr. D. E. Jewitt for his help with the manuscript and to the Department of Morbid Anatomy and Chemical Pathology for their help.

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# Lipoprotein levels in apparently healthy men and women in the west of Scotland

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*Lipoprotein typing was undertaken in apparently healthy women (419) and men (103) in whom measurements of fasting total cholesterol, triglycerides, and cholesterol content of the major lipoprotein fractions were made.*

*In the female group (30 to 59 years) there was a significant rise in total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides with age. Using total cholesterol and triglyceride levels for classification, type II hyperlipoproteinaemia was present in 1 per cent and type IV in 6·7 per cent. When LDL cholesterol levels were also considered, type II occurred in 9·8 per cent (8·4% type IIA and 1·4% type IIB).*

*In the male group (40 to 59 years) there was no increase in cholesterol or triglyceride levels with age: 11 per cent had type IV hyperlipoproteinaemia and none had a type II abnormality. When LDL cholesterol levels were also considered, type II occurred in 3 per cent (2% type IIA and 1% type IIB).*

*The apparent increase in LDL cholesterol and frequency of type IIA abnormality in women could be merely the consequence of arbitrary selection of upper limits of normality for LDL cholesterol, but may signify improved detection of a high risk group.*

Previous surveys have identified raised cholesterol and/or triglyceride concentrations as risk factors for coronary heart disease (Blackburn, 1970; Carlson and Böttiger, 1972). Prospective studies suggest that the degree of rise is of prognostic value (Carlson and Böttiger, 1972; Keys, 1970; Kannel *et al.*, 1971). In addition, reports indicate that low density lipoprotein (LDL), as measured by its cholesterol content, may be a more important prognostic factor for coronary heart disease than total cholesterol (Slack, 1969).

An earlier study of 4496 apparently healthy male subjects at work in the west of Scotland showed that 15·3 per cent had a lipoprotein abnormality as indicated by a rise in plasma cholesterol and/or triglyceride. This study has been extended to assess the frequency of lipoprotein abnormalities when measured by LDL cholesterol levels, in addition to total cholesterol and triglycerides, in a group of female and male subjects.

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## Patients and methods

The group consisted of 419 women and 103 men, whose ages ranged between 35 and 60 years. All worked in a light engineering factory and were distributed approximately equally between light manual and non-manual work. The response rate was 59·6 per cent.

Before attending the screening unit each subject was given a standardized questionnaire on history of chest pain (Rose and Blackburn, 1968a), smoking habits, and bronchitis (Medical Research Council, 1965). At the screening unit the procedure was as described by Hawthorne, Gillis, and McLean (1972): height, weight, blood pressure, and a standard six limb-lead electrocardiogram were recorded (Rose and Blackburn, 1968b).

After an overnight fast, 10 ml blood were drawn, without venous stasis, into lithium sequestrene (1 g/l). Plasma was separated and stored at 4°C before analysis. Plasma total cholesterol and triglycerides were measured by autoanalyser techniques

(Annan and Isherwood, 1969; Kessler and Lederer, 1965) and lipoprotein electrophoresis carried out on paper using albuminated buffer (Lees and Hatch, 1963). Those subjects whose electrophoretic pattern showed chylomicra were excluded. The cholesterol content of each major lipoprotein fraction of plasma was estimated by the precipitation technique of Burstein, Scholnick, and Morfin (1970). This technique had previously been compared with the ultracentrifugal fractionation method of Fredrickson, Levy, and Lees (1967). Plasma samples from 40 patients with a variety of lipoprotein levels were fractionated by both methods; the mean VLDL, LDL, and HDL cholesterol levels were similar for each method.

Initially each subject was assigned two phenotypes, using the upper limits of normal reported by Fredrickson *et al.* (1967) in a North American population, and the classification suggested by Beaumont *et al.* (1970). It was assumed that a rise in total cholesterol, alone, signified a raised LDL cholesterol. Similarly, a triglyceride level above the accepted limits signified a raised VLDL content in the plasma. No attempt was made to classify subjects with increases of both cholesterol and triglyceride. The additional data obtained from lipoprotein precipitation allowed a second phenotype to be assigned to each subject. A raised LDL cholesterol was indicative of type II hyperlipoproteinaemia. Subjects with raised total cholesterol and triglyceride were assessed on the basis of LDL cholesterol and classified as type IIB or type IV phenotype as appropriate. The classification and criteria are shown in Table 1.

In 65 (11%) subjects there was insufficient plasma for precipitation of all fractions. In these subjects total cholesterol and VLDL cholesterol were measured, but a high density lipoprotein (HDL) cholesterol level of 1·3 mmol/l was assumed; LDL cholesterol was then calculated.[1] In a series of 300 comparisons no significant difference was found in LDL cholesterol values obtained using a measured or 'assumed' HDL cholesterol value (Ballantyne and Jubb, in preparation).

Subjects with chylomicra in their plasma were assumed to be non-fasting and were excluded; this means that any type I and V subjects, together with the non-fasting population, have not been considered. There were three such subjects. Type III abnormality is rare and was not sought in this study.

## Normal and abnormal participants

The total population was divided into four subgroups: female normal and abnormal, male normal and abnormal—according to the criteria used in our previous survey (Lorimer *et al.*, 1974). Subjects were regarded as abnormal who were in one or more of the following categories: smoking more than 5 cigarettes per day; more than 10 per cent above ideal weight for age; hypertensive, i.e. systolic

TABLE 1 *Criteria for establishing lipoprotein phenotypes*

| *Classification based on total cholesterol and triglyceride levels* | | | *Classification based on LDL cholesterol and triglyceride levels* | | |
|---|---|---|---|---|---|
| *Type* | *Lipid levels* | | *Type* | *Lipid levels* | |
| Normal | Total cholesterol | N | Normal | Total cholesterol | N |
| | Triglyceride | N | | LDL cholesterol | N |
| | | | | Triglyceride | N |
| II | Total cholesterol | ↑ | IIA | Total cholesterol | N or ↑ |
| | Triglyceride | N | | LDL cholesterol | ↑ |
| | | | | Triglyceride | N |
| | | | IIB | Total cholesterol | N or ↑ |
| | | | | LDL cholesterol | ↑ |
| | | | | Triglyceride | ↑ |
| IV | Total cholesterol | N | IV | Total cholesterol | N or ↑ |
| | Triglyceride | ↑ | | LDL cholesterol | N |
| | | | | Triglyceride | ↑ |
| Not classified | Total cholesterol | ↑ | | | |
| | Triglyceride | ↑ | | | |

*Notes*: Subjects with chylomicra at origin on paper electrophoresis were excluded as non-fasting (or Type I or V). Type III has not been considered because of its rarity.
*Abbreviations*: N=normal; ↑=raised.

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[1] LDL cholesterol=Total cholesterol—(VLDL cholesterol + 1·3) mmol/l.

TABLE 2 *Health survey in west of Scotland*

| *Classification* | *Male* (%) | *Female* (%) |
|---|---|---|
| Normal | 17·5 | 30·4 |
| Abnormal | 79·5 | 69·6 |
| Non-fasting | 3·0 | — |

TABLE 4 *Lipoprotein abnormalities in apparently healthy women*

| *Age group* | *No. of subjects* | *Classification by total cholesterol and triglyceride** *Type II A* | *B* | *Type IV* | *Total* | *Classification by LDL cholesterol and triglyceride** *Type II A* | *B* | *Type IV* | *Total* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Total population* | | | | | |
| 30–39 | 58 | 3·5 | 0 | 3·5 | 7·0 | 3·5 | 1·6 | 3·5 | 8·6 |
| 40–49 | 188 | 0·5 | 0 | 9·1 | 9·6 | 9·0 | 1·5 | 7·5 | 18·0 |
| 50–59 | 173 | 0·6 | 0 | 5·2 | 5·8 | 9·8 | 1·2 | 4·6 | 15·6 |
| | | | | *Normal population* | | | | | |
| 30–39 | 21 | 5·0 | 0 | 5·0 | 10·0 | 5·0 | 5·0 | 0 | 10·0 |
| 40–49 | 52 | 0 | 0 | 3·3 | 3·3 | 3·8 | 1·9 | 1·9 | 7·6 |
| 50–59 | 54 | 1·7 | 0 | 1·7 | 3·4 | 9·3 | 1·7 | 1·7 | 12·7 |
| | | | | *Abnormal population* | | | | | |
| 30–39 | 37 | 0 | 0 | 5·4 | 5·4 | 0 | 0 | 5·4 | 5·4 |
| 40–49 | 136 | 0·8 | 0 | 11·0 | 11·8 | 11·0 | 1·5 | 10·2 | 22·0 |
| 50–59 | 119 | 0·8 | 0 | 6·0 | 6·8 | 8·4 | 0·8 | 5·0 | 14·0 |

*Per cent of subjects classified in each lipoprotein type.

blood pressure >170 mmHg or diastolic blood pressure >100 mmHg; electrocardiographic abnormalities present (types I and II in Minnesota code); a history suggestive of angina or myocardial infarction. The number of subjects in each subgroup is shown in Table 2.

## Results

### Female population

Fasting lipid levels were available in 419 female subjects (127 normal and 292 having one or more abnormality as previously defined). In these subgroups results for total cholesterol, LDL cholesterol, and triglyceride were considered in relation to age. These data are presented in Table 3. None of the subjects was taking an oral contraceptive agent at the time of sampling. The number of post-menopausal subjects is unknown.

In the total female population there was a significant rise in cholesterol, LDL cholesterol, and triglyceride with age. In addition, the triglyceride levels obtained in the abnormal group were significantly higher ($P < 0{\cdot}01$) than in age-related 'normal' subjects. The 'abnormal' group includes those subjects who were obese, either as a single abnormality or together with other abnormalities. The obese, but otherwise normal group was small and could not be analysed independently.

These lipid values were used as the basis for typing of hyperlipoproteinaemia. The upper limits of normal used were those reported by Fredrickson *et al.* (1967) in a North American population. As previously described, phenotypes were assigned in two ways: firstly, from levels of total cholesterol and triglyceride; secondly, using the additional information obtained from the LDL cholesterol levels. Results are shown in Table 4.

The initial classification indicated that type IV pattern occurred most frequently, 6·7 per cent of all subjects falling into this group. When LDL cholesterol levels were also considered, it was found that 6 subjects (21% of type IV group) could be reclassified as type IIB. The use of all available data indicates that 2·4 per cent of the 'normal' women compared with 7·5 per cent of the 'abnormal' group showed type IV hyperlipoproteinaemia.

When total cholesterol and triglyceride levels were used as the basis for classification, type II hyperlipoproteinaemia was present in 1 per cent. When LDL cholesterol levels were also considered, the frequency of type II patterns rose to 9·8 per cent

TABLE 3 *Levels of total cholesterol, LDL cholesterol, and triglyceride (mmol/l) in apparently healthy women*[1]

| *Age group* | *Total population* *No.* | *Total cholesterol* | *LDL cholesterol* | *Triglyceride* | *Normal* *No.* | *Total cholesterol* | *LDL cholesterol* | *Triglyceride* | *Abnormal* *No.* | *Total cholesterol* | *LDL cholesterol* | *Triglyceride* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30–39 | 58 | *5·2±0·9 | 3·5±0·9 | 0·9±0·4 | 21 | 5·2±0·8 | 3·6±0·9 | 0·9±0·5 | 37 | 5·2±0·9 | 3·6±0·7 | 0·9±0·4 |
| 40–49 | 188 | 5·6±0·9 | 3·9±0·9 | 1·1±0·5 | 52 | 5·5±0·7 | 3·9±0·7 | 0·9±0·4 | 136 | 5·7±0·9 | 3·9±0·9 | **1·2±0·5 |
| 50–59 | 173 | ***6·2±1·0 | 4·4±1·0 | 1·2±0·6 | 54 | ***6·2±1·1 | 4·5±1·0 | 1·1±0·5 | 119 | 6·3±1·0 | 4·4±1·0 | **1·3±0·6 |

*Significance of differences*: *$P<0{\cdot}02$ when compared with age 40 to 49; **$P<0{\cdot}01$ when compared with normals of same age; ***$P<0{\cdot}001$ when compared with age 40 to 49.

[1] Mean ± SD is shown.

(8·4% type IIA and 1·4% type IIB). The type IIB group included subjects, initially classified as type IV, who showed a rise in LDL cholesterol but had normal total cholesterol, and also subjects with raised total cholesterol, triglycerides, and LDL cholesterol. From analysis of total cholesterol, triglyceride, and LDL cholesterol, 8·6 per cent of the 'normal' and 10·5 per cent of the 'abnormal' had a type II abnormality; this difference was not statistically significant.

### Male population

Similar data were available for 103 male subjects aged between 40 and 59 years. Three subjects with chylomicra were assumed to be non-fasting and were excluded. Of the remaining 100 subjects, 18 were considered 'normal' and 82 'abnormal', using the previously defined criteria.

There was no significant difference in total cholesterol, LDL cholesterol, or triglycerides ($P > 0{\cdot}01$) between the two age groups (Table 5). The small number of normal subjects did not allow comparison of subgroups.

Using total cholesterol and triglyceride levels as the basis for hyperlipoproteinaemia typing, it was found that 11 per cent of subjects had a type IV pattern. When LDL cholesterol levels were included, one subject was reclassified as type IIB, reducing the frequency of type IV to 10 per cent. It should be noted that obese subjects (32%) have not been excluded, though previous experience suggests that these subjects are contributing to the presence of type IV pattern.

When total cholesterol levels alone were considered, no subject could be classified as type II. However, with the inclusion of LDL cholesterol levels 2 per cent of subjects had type IIA and 1 per cent type IIB abnormalities (Table 6).

## Discussion

The frequency with which hyperlipoproteinaemia occurs in any population is dependent on arbitrary limits selected by the investigators. Fredrickson *et al.* (1967) reported that the age-related levels for men and women followed a similar pattern and suggested that differences between the sexes could, for practical reasons, be ignored except in the case of HDL cholesterol. More recent evidence suggests that there may be significant differences in cholesterol and triglyceride levels between men and women (Brown and Daudiss, 1973; Lewis *et al.*, 1974).

The present study showed a significant increase in total cholesterol, LDL cholesterol, and triglyceride with age in the female group. These data show that this rise is the result of an increase in LDL cholesterol, since no significant changes were found in VLDL and HDL cholesterol levels. Oral contraceptive preparations are associated with rises in triglycerides and HDL cholesterol, but none of our population was taking one of these; normal HDL values were found in all subjects during this study. It might be expected that a rise in triglyceride would be reflected in an increased VLDL cholesterol concentration. However, the absolute increases in triglyceride were such that as little as 0·078 mmol/l change in VLDL cholesterol concentration would be expected and this is beyond the precision of the methods used in this study.

These results for women contrast with our previous report on men in the same area, when no significant change in lipid levels was noted with age (Lorimer *et al.*, 1974), a finding that is confirmed in our current smaller series. Results obtained on the male population corroborate those previously reported, in that total cholesterol does not rise with age over 40 years; in the present study, this was also found to be true of LDL cholesterol levels.

The triglyceride levels in men were significantly higher than those in women, both in the total population and in those considered normal by our criteria. These findings are in keeping with those reported by Brown and Daudiss (1973) and Wood

TABLE 5 *Levels of total cholesterol, LDL cholesterol, and triglycerides (mmol/l) in apparently healthy men*[1]

| *Age group* | *No.* | *Total population* *Total cholesterol* | *LDL cholesterol* | *Triglyceride* |
|---|---|---|---|---|
| 40–49 | 33 | 5·4±0·9 | 3·6±0·9 | 1·3±0·6 |
| 50–59 | 67 | 5·7±0·9 | 3·8±0·9 | 1·3±0·5 |

[1] Mean ± SD is shown.

TABLE 6 *Lipoprotein abnormalities in apparently healthy men*

| *Age group* | *No. of subjects* | *Classification by total cholesterol and triglyceride** | | | | *Classification by total and LDL cholesterol and triglyceride** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Type II A* | *B* | *Type IV* | *Total* | *Type II A* | *B* | *Type IV* | *Total* |
| 40–49 | 33 | 0 | 0 | 18·2 | 18·2 | 0 | 3·0 | 15·2 | 18·2 |
| 50–59 | 67 | 0 | 0 | 8·9 | 8·9 | 3·0 | 0 | 8·9 | 11·9 |

*Per cent of subjects classified in each lipoprotein type.

*et al.* (1972). It has been suggested that measurement of LDL cholesterol is more indicative of the risk of subsequent coronary heart disease than is measurement of total cholesterol. It seemed of importance to assess whether or not this measurement increased the yield of subjects at risk. In women, the initial classification of phenotypes, using the same upper limits of normal for total cholesterol and triglyceride as reported by Fredrickson *et al.* (1967), indicated type II abnormality in 1 per cent, with type IV being more frequent (6·7%). However, classification using in addition LDL cholesterol levels increased the frequency of type II and decreased that of type IV. This increased frequency of type II (from 0·8 to 11%) was especially obvious at age 40 to 49 years. It may be relevant that this is the age at which clinical manifestations of coronary heart disease begin to increase in women. Oliver (1974) has recently reported a series of 145 women with ischaemic heart disease who were under 45 years of age; when lipoprotein classification was undertaken, type IIA was the commonest abnormality found.

The significance of this apparent increase in the presence of type II abnormality when LDL cholesterol measurements are made is, however, not yet certain. It may be that the upper limits of normal used are too low for women or that our population differs from that reported from the United States and whose upper normal limits we have used. Nevertheless it is interesting to note that female populations studied in the United Kingdom and United States reveal similar age-related changes in the lipid levels measured, though absolute values differ (Brown and Daudiss, 1973). Alternatively, it may be that the use of LDL cholesterol values does indeed define a high risk group of subjects with respect to subsequent coronary heart disease. Long-term follow-up studies are required to confirm or refute this possibility.

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# Discriminant function analysis of factors related to myocardial infarction in male patients on antihypertensive therapy

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*Records of 367 male patients who began attending the Dunedin Hospital Hypertension Clinic between 1959 and 1969 were coded up to the end of 1972. Of these patients, 60 had their first myocardial infarction, or sudden cardiac death without previous evidence of myocardial infarction, while they were attending the clinic. This infarct group was compared with a control group of 120 which was chosen from the remaining patients so that the two groups would be comparable with regard to their age and year of first attendance. A stepwise discriminant function analysis showed that the basal systolic and diastolic pressures measured when patients started attending the clinic were the variables with the most significant difference. Further analysis showed that inclusion of the average casual standing systolic pressure when patients were receiving antihypertensive therapy improved the discrimination between the groups. The average casual standing diastolic pressure during antihypertensive therapy also improved the discrimination, but, curiously enough, with a negative sign in the discriminant function. Quetelet's index of obesity similarly improved the discrimination, obese subjects having less risk of infarction or sudden death. Serum cholesterol, however, was not related to prognosis.*

Prospective studies have shown that individuals with hypertension have a higher risk of developing cardiovascular disease than individuals with lower levels of blood pressure (Kannel, 1975). There is also evidence that the treatment of hypertension reduces the incidence of some forms of cardiovascular disease including strokes and congestive heart failure (Veterans Administration Cooperative Study Group, 1967, 1970, 1972). However, doubt remains about the effect of treatment for hypertension on the incidence of myocardial infarction and sudden coronary deaths. In view of this, it was decided to study the records of patients being treated for hypertension and who experienced myocardial infarctions or sudden cardiac deaths. A comparison could then be made with control patients who were also receiving treatment for hypertension, but who had not had myocardial infarctions or sudden cardiac deaths before the end of the study period.

## Patients and methods

The patients studied were the 493 male patients who started attending the Dunedin Hospital Hypertension Clinic in the years 1959 to 1969. A total of 126 of these patients were not included in the analysis because they were over 70 when first seen, or were assessed but not treated, or had some other disease not related to hypertension when they first attended. The records of the remaining 367 patients were coded for computer analysis. Among the data items coded, the following have been used in the present analysis.

### Patient identification

**Initial investigations** Weight, height; casual lying systolic and diastolic blood pressure; basal lying systolic and diastolic blood pressure.

**Continuing investigations** Cholesterol, urea; casual standing systolic and diastolic blood pressure (either a single reading or the first reading at a half-day test). If there were more than one half-day test

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recorded in any month, the first one was used. If there were no half-day tests in a given month then the first single casual pressure recorded in the month was taken.

**Clinical events** Myocardial infarction, established stroke, cause of death.

This coding was done retrospectively in 1973, but the format of the clinical records of patients attending this clinic had ensured that a high proportion of the relevant data was available.

Among the 367 patients studied, there were 60 who either had their first myocardial infarction (determined by standard electrocardiographic criteria) while attending the clinic, or who had sudden deaths (usually, but not invariably, with antecedent chest pain) without previous evidence of myocardial infarction. In 7 cases there was some doubt with regard to their inclusion. Four of these had possibly had earlier myocardial infarctions. In the other 3 cases, evidence for a cardiac cause of death was not definite. This doubtful group of 7 did not differ significantly from the remaining 53 as far as the variables used in the analysis were concerned, and they were, therefore, included. However, no patient who had a major stroke before his first myocardial infarction or sudden death, and no patient who had attended for less than 12 months before his first myocardial infarction or sudden death, was included. Of the 60 patients in the group, 33 died suddenly or within one month of the infarct. Most deaths occurred out of hospital and there were only 9 necropsies in these 33 patients.

A control group was selected from the remaining patients in a manner that would avoid confounding the effects of age and changes in patient management, which may have occurred over the study period.

The following arbitrary control-selecting function was used:

matchscore = 3 × absolute difference in year of first attendance + absolute difference in year of birth.

A control was selected for each infarct patient by random selection from those non-infarct patients with whom he had a minimum matchscore, excluding any patient who had a major stroke. The process was then repeated once, so as to give a control group of 120 patients. The mean age of the infarct patients at their first attendance was 58·0 years, and that for the controls 56·8 years. The average date of first attendance for both groups was in the first half of 1963. The infarct group and the control group are thus comparable as far as age and year of first attendance at the Hypertension Clinic are concerned.

The variables used in analysis are defined as follows:

*ASYS:* For an infarct patient, this is the average casual standing systolic blood pressure for the 12 months before the month in which he had a myocardial infarction or sudden cardiac death. For a control group patient, it is a similar average of twelve months' casual standing systolic recordings. The period chosen corresponds to the same duration of attendance as that from which ASYS was obtained for the infarct patient with whom he was matched.

*ADIA:* The average casual standing diastolic pressure corresponding to ASYS.

*BSYS:* The basal systolic blood pressure which is measured in the following manner. The patient is admitted to a hospital single room at about 8 p.m. At 10 p.m. he is given 0·2 g pentobarbitone by mouth; if the patient is awake during the night, a further dose of 0·1 g pentobarbitone is given, but not later than 4·30 a.m. A technician enters at 7.30 to 8.00 a.m. and, without conversing, records the patient's blood pressure every minute for 15 to 20 minutes. The lowest systolic pressure recorded is selected as BSYS.

*BDIA:* The diastolic pressure corresponding to BSYS. Most patients had either not had previous treatment for hypertension, or they had their treatment stopped before the basal recordings were taken. However, 3 of the 60 infarct patients, and 8 of the 120 control patients were on some antihypertensive treatment at the time of their basal recordings.

*CSYS:* The casual lying systolic blood pressure recorded during a patient's first attendance at the clinic.

*CDIA:* The diastolic pressure which corresponds to CSYS.

*CHOL:* The average serum cholesterol recorded up to the month of myocardial infarction or sudden death. For a control patient, it is the average cholesterol in the period corresponding to that from which CHOL was obtained for the patient used to select him. Cholesterols were not routinely obtained until 1963 and, particularly in the first few years it was measured, some patients may not have been fasting when blood samples were obtained. However, because of the fact that the infarct and control group are comparable as far as year of first attendance is concerned, it is unlikely that any bias has been introduced.

*UREA:* The serum urea value obtained when a patient first attended the clinic.

*QUET:* Quetelet's index, obtained from a patient's weight in grams when he first attended, divided by the square of his height in centimetres.

The method of analysis used was stepwise discriminant analysis, a good account of which is given by Affi and Azen (1972). The objective of the method in the present context is to select variables which show the most significant difference between the infarction and control groups. At each step, the variable selected is the one that gives the greatest improvement in discrimination, given those variables already selected. The computer programme used for this analysis belongs to the BMD package (Dixon, 1967).

Missing values were dealt with by the method of mean substitution (Chan and Dunn, 1972). A patient in the infarct group who had a missing value for a variable was assigned the mean of that variable for infarct patients, and missing values in the control group were assigned means for the control group. The discriminant analysis was also done a second time with missing values being assigned the overall means for the two groups combined. The results did not affect the conclusions made and so the results of the first analysis only will be presented.

## Results

The means of the variables for the 60 patients in the infarct group and the 120 patients in the control group are shown in Table 1, together with the number of missing values for each variable. The F values obtained during the first step of the discriminant function analysis programme are shown in Table 2. The largest F value is that for the basal diastolic blood pressure, which, therefore, gets selected first into the discriminant function. It should be noted that the F value for the basal systolic blood pressure is almost as large; the fact that the basal diastolic gets selected first does not mean that it is a significantly better discriminator than the basal systolic. Among the other entries in Table 2, it can be seen that the differences between the groups in the means of the variables ASYS and CSYS are also statistically significant. The remaining variables do not show significant differences when they are considered independently. In particular, it can be seen that ADIA and CHOL fall into this category.

TABLE 1 *Mean values for infarct group and control group, together with number of missing values of each variable*

| *Variable* | *Means in infarct group* | *Means in control group* | *No. of missing values* |
|---|---|---|---|
| BSYS | 160·8 | 146·6 | 5 |
| BDIA | 102·8 | 93·7 | 5 |
| CHOL | 243·7 | 238·8 | 35 |
| UREA | 40·9 | 39·3 | 0 |
| QUET | 2·61 | 2·68 | 36 |
| CSYS | 206·6 | 196·2 | 3 |
| CDIA | 121·1 | 116·0 | 3 |
| ASYS | 157·3 | 149·9 | 6 |
| ADIA | 97·1 | 97·6 | 6 |

TABLE 2 *F values obtained in first step of stepwise discriminant function analysis and statistical significance*

| *Variable* | *F values* | *Statistical significance P<* |
|---|---|---|
| BDIA | 14·9 | 0·01 |
| BSYS | 13·4 | 0·01 |
| ASYS | 7·9 | 0·01 |
| CSYS | 5·6 | 0·05 |
| CDIA | 3·6 | |
| QUET | 2·1 | |
| CHOL | 0·7 | |
| UREA | 0·3 | |
| ADIA | 0·1 | |

The F values obtained in the fourth step of the analysis are shown in Table 3. Four variables have been entered into the discriminant function in the order in which they are presented in this table: BDIA, ASYS, ADIA and QUET. The analysis must stop here as none of the F values for the variables not entered approaches statistically significant levels. In contrast, the F values for the variables entered are all significant beyond the 0·01 probability level.

In a separate analysis, the linear discriminant

TABLE 3 *F values obtained in fourth step of discriminant function analysis for variables entered into discriminant function, and for those not entered*

| *Variable entered* | *F values* | *Statistical significance P<* |
|---|---|---|
| BDIA | 19·3 | 0·01 |
| ASYS | 14·0 | 0·01 |
| ADIA | 8·9 | 0·01 |
| QUET | 7·3 | 0·01 |
| *Not entered* | | |
| CHOL | 1·1 | |
| UREA | 1·1 | |
| BSYS | 0·8 | |
| CDIA | 0·6 | |
| CSYS | 0·1 | |

function involving the variables ASYS and ADIA was found to be 2·2 ASYS to 2·3 ADIA. In other words, the best linear discriminator involving these two variables alone is the pulse pressure. It has already been found (Table 1) that ADIA has approximately the same mean in the two groups. It was not until ASYS had been entered into the discriminant function in the stepwise procedure that it became apparent that ADIA would also be included.

Finally, the relation of the variables with the severity of infarction was investigated by considering those patients who had sudden deaths, or who died within one month of their myocardial infarction. Altogether 33 patients fall into this category and their means are compared with the means for the controls selected along with them in Table 4. A similar comparison involving the remaining 27 infarct patients is also presented in this table. It can be seen that many of the differences between infarct and control groups are more pronounced in the infarct patients who died within one month. Stepwise discriminant analysis for this group of 33 with their 66 controls followed a pattern similar to that presented for the whole group. In contrast, the stepwise analysis for those who did not die within one month stopped after basal diastolic was placed in the discriminant function. Numbers are inadequate to warrant presenting separate discriminant analysis results, but it is apparent that the differences between the infarct group and the control group can be largely attributed to patients with more severe disease who died within one month of their first myocardial infarction, or who had sudden cardiac deaths without previous myocardial infarction.

TABLE 4 *Mean values for infarct patients who died within one month, and for those who survived more than one month.*

| *Variable* | *Patients (33) who died within one month* | *Patients (27) who survived at least one month* |
|---|---|---|
| BSYS | 168·1 (147·7) | 151·9 (145·3) |
| BDIA | 103·4 (93·7) | 102·0 (93·7) |
| CHOL | 247·2 (234·7) | 237·9 (244·8) |
| UREA | 44·1 (39·1) | 37·0 (39·6) |
| QUET | 2·58 (2·69) | 2·64 (2·66) |
| CSYS | 210·9 (195·4) | 201 4 (197·2) |
| CDIA | 117·9 (113·9) | 125 0 (118·4) |
| ASYS | 160 8 (150·5) | 153·3 (149·1) |
| ADIA | 95·1 (97·0) | 99·4 (98·3) |

*Note:* Variable means for relevant control groups are shown in parentheses.

## Discussion

Considerable speculation has centred on the effect of antihypertensive treatment on the incidence of coronary heart disease. The known effect of treatment on the incidence of other forms of cardiovascular disease makes it unethical to conduct controlled trials for anything but very mild hypertension. Such studies also require large numbers of patients (Peart, 1973) and negative findings will not prove that the treatment of more severe hypertension does not reduce the incidence of coronary heart disease. It is felt that the results we have presented indicate that valuable information in this regard may be obtained by studying patients already receiving treatment for their hypertension.

The study of prognosis of hypertension is complicated by the possibility of confounding the effects of age with the effects of other variables. Kleinbaum *et al.* (1971) attempted to solve this problem by including second order product terms in their stepwise discriminant analysis and found that diastolic blood pressure, age, and cholesterol × age, were chosen for their discriminant function. Unfortunately, product terms of this nature pose difficulties in interpreting the results of analysis. We have avoided this problem by selecting a control group which is comparable with the infarct group as far as age and year of first attendance at the clinic are concerned.

The measurement of the basal blood pressure (Alam and Smirk, 1943) when patients first attend has been the practice at the Dunedin Hospital Hypertension Clinic for many years (Smirk, 1957; Smirk, Veale, and Alstad, 1959; Hodge and Smirk, 1967). The present results once again confirm its usefulness as a measure of the severity of hypertension. In particular, it is a considerably better indicator of the risk of coronary heart disease than the first casual recording.

The relation between the risk of infarction and blood pressure levels on treatment is of greater importance. The results we obtained indicate that the average standing systolic blood pressure on treatment is related to the incidence of myocardial infarction and sudden cardiac death. On the other hand, the average standing diastolic blood pressure does not discriminate between the groups when it is considered on its own. Beevers, Fairman, and Harpur (1973) also found that the control of hypertension as measured by the average diastolic blood pressure was not related to the incidence of myocardial infarction. Breckenridge, Dollery, and Parry (1970) considered the average systolic and diastolic blood pressures on treatment and showed that there were no consistent differences between patients dying from uraemia, cerebrovascular disease, or myocardial infarction. However, they found that problems of handling large amounts of data prevented comparison between these patients and the rest of their clinic patients.

In spite of the fact that the average diastolic pressure does not discriminate between our two groups, we found that the average pulse pressure (i.e. the difference between the average systolic and diastolic pressures) improves the discrimination achieved by the average systolic alone. It is of interest to note that Kannel, Gordon, and Schwartz (1971b) found that the diastolic blood pressure generally had a negative sign in their discriminant functions. However, in their untreated population, the pulse pressure did not give a better discrimination than the systolic pressure. Our own findings relating to pulse pressure must be interpreted with some caution, because its mean difference between the groups is not much greater than that for the systolic pressure alone (Table 1). Before attaching too much significance to it, the sort of analysis we have done must be replicated in studies involving other patients.

It is of particular interest that the average blood pressures when patients are receiving antihypertensive therapy are included in the discriminant function, even though a basal pressure has already been selected. This suggests that, even allowing for differences before treatment, the degree of control of hypertension by therapy affects the incidence of myocardial infarction and sudden coronary death. A separate analysis (Smith, 1975) showed that patients with an average systolic pressure below 170 mmHg all had approximately the same risk of infarction, but a patient with an average systolic pressure above this level was exposed to a greater risk. An even greater risk differential was found when comparing those with an average pulse pressure above 70 mmHg with those whose average pulse pressure was below 70 mmHg. These levels were calculated using all 367 patients in this study with all ages pooled, and a larger number of cases is required to determine their relation to age.

We were also interested to find that Quetelet's index gets included in the discriminant function by the stepwise analysis. Its very low correlation with height in our patients of −0·08 is close to that found in other studies (Goldbourt and Medalie, 1974). It appears in the discriminant function with a negative sign after the basal and average treatment levels have been included. The implication is that, for given pre-treatment and treatment blood pressure levels, the more obese the patient the less likely he is to have a coronary event. This result must be interpreted with some caution as there are a considerable number of missing values for this variable (Table 1). Account must also be taken of the fact that obesity commonly has a negative correlation with smoking (Keys *et al.,* 1972). We did not have adequate data to include smoking in our analysis and it may be that the apparent association of prognosis with obesity is in fact the result of the effects of smoking. However, there are some previous reports that suggest that in hypertension, particularly in women patients, obesity is associated, with a better prognosis (Simpson and Gilchrist, 1958; Nye, 1964).

The fact that serum cholesterol is not included in the discriminant function warrants some comment. Kannel *et al.* (1971a) found that raised serum cholesterol level is associated with an increased incidence of coronary heart disease in the Framingham study but this association occurred predominantly in the younger age-groups. In the 50 to 62 year age-group, on the other hand, the difference in the mean cholesterol between their coronary heart disease group and their non-coronary heart disease group was only 0·39 mmol/l (15·4 mg/100 ml) (Kannel *et al.,* 1971a). A study of the regression coefficients they obtained also indicates that, though the cholesterol levels were related to the incidence of cardiovascular disease, their relation to cardiovascular mortality was not significant (Kannel and Dawber, 1974). Our own results indicate that it is not a useful predictor of the incidence of myocardial infarction and sudden cardiac deaths in male patients on antihypertensive therapy.

Another variable which has been used as a prognostic indicator in hypertension is retinal grade. This variable was included in our first stepwise discriminant analysis, but at no stage did it look likely to be selected for the discriminant function. The fact that it is a discrete variable means that it should not be included in a stepwise discriminant function analysis, unless the sole purpose is to obtain a predictive formula. Because of this, a separate analysis was done using a stepwise information theory analysis (A. H. Smith and P. V. de Souza, unpublished observations). This also gave the impression that blood pressure measurements are considerably better prognostic indicators than the retinal grade.

Finally, it was shown that the differences in blood pressure levels between the infarct patients and the controls were greatest for those who had sudden coronary deaths or who died within one month of their first myocardial infarction. In fact, the discrimination achieved between those who had a myocardial infarct and survived more than one month and their control group is not good and involves the basal diastolic pressure alone. The numbers studied are small, but it appears that one of the effects of adequate control of blood pressure is to reduce the incidence of sudden coronary deaths and myocardial infarctions which are fatal within one month.

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*British Heart Journal*, 1976, **38**, 1200–1203.

# Coronary angiography
## *Review of 1500 consecutive cases* [1]

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*From Harefield Hospital, Harefield, Middlesex*

*Fifteen hundred coronary angiograms have been performed by the staff of Harefield Hospital since 1970. Only 2 deaths have occurred in the last 1000 consecutive cases though there were 5 in the first 500 cases. This drop in the mortality is ascribed to careful attention to detail and better training of the operators. It is concluded that the Judkin's method of coronary angiography* in trained hands *is a safe method of investigation but that because of the very serious potential dangers it is unjustifiable for new units to start unless there is a fully experienced investigator in charge.*

With the advent of successful revascularization of blocked and narrowed coronary arteries, using venous bypass grafts from the aorta, the demand for coronary angiography has risen rapidly during the past 5 years. At Harefield 25 arteriograms were performed in 1970 but 615 in 1975 (Fig. 1) though circumstances beyond our control reduced the number conspicuously at the end of the last year. Information about the safety of this examination is, therefore, important.

Emanuel (1975) circularized 50 British centres undertaking coronary angiography in 1973. Of the 46 who replied, only 9 knew the mortality rate for their institution; the highest was up to 0·6 per cent. The morbidity ranged from 0·9 to 2·2 per cent. In 1973, Petch, Sutton, and Jefferson reported a series of 400 angiograms with an overall mortality of 1·5 per cent; 2·4 per cent for the 248 done by Judkins' (1967) method and a zero mortality for the 111 by Sones and Shirey's (1962) method. Adams, Fraser, and Abrams (1973), in a nationwide survey of the United States, found a 0·8 per cent mortality for Judkins' technique and a 0·13 per cent mortality for Sones'.

The purpose of this paper is to review our experience with particular reference to complications.

**Coronary angiography at Harefield Hospital**
Originally, coronary angiograms were carried out by whichever investigator, consultant, or registrar was on rota for that day. Our morbidity and mortality (2%) was unacceptably high so the policy was changed and only 2 consultants, 1 in cardiology and 1 in radiology, undertook coronary angiography, with a registrar assisting. This continued until more experience had been gained. The coronary team was then increased to include first the senior registrar and then registrars. At present we have 3 consultants, 1 senior registrar, and 2 registrars allowed to undertake coronary angiography unsupervised. This gives an average of

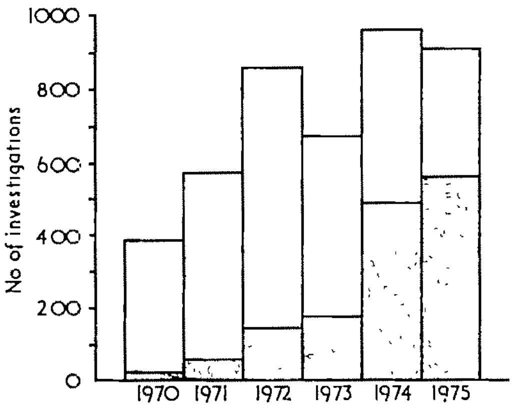

FIG. 1 *Cardiac investigations performed each year at Harefield Hospital. The shaded blocks represent coronary angiogram and the open columns the investigations undertaken without coronary angiography.*

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[1] Based on a paper given to the Third European Congress of Radiology in Edinburgh in June 1975.

100 angiograms per year per operator in this hospital. One consultant also catheterizes elsewhere. In addition, a physician and/or his registrar from a neighbouring hospital catheterizes up to 2 patients once a week. These latter have not been included in the study.

There is only one room suitable for doing coronary angiograms in the hospital. This is equipped with pulsed cine, a high definition caesium iodide intensifier, and high speed tubes, as well as a biplane roll film changer. It has to cope with most of the other cardiac investigations as well, including the children.

A second room with non-pulsed cine and an ordinary intensifier is available for other investigations, such as pacemaker procedures and pulmonary angiograms.

The number of investigations which do not include coronary angiography (Fig. 1) has declined since 1972. This is probably because of the greater readiness to undertake coronary angiography in patients suspected of having predominantly a non-ischaemic diagnosis. For instance, all patients with aortic valve disease now have coronary angiograms performed routinely as well as those with cardiomyopathy. Routine re-examination of patients after coronary artery bypass grafting also accounts for a substantial number of patients (Fig. 2).

The age distribution shown in Fig. 3 has not changed significantly over the years and is predominantly in the sixth decade. The male and female ratio has also remained steady at approximately 5:1.

## Angiographic method

Patients are all premedicated with atropine and diazepam (Valium) or papaveretum and hyoscine. The Judkins technique is used routinely and in only 21 patients has this proved impossible (1·4%). Patients are *x*-rayed on a rotating cradle (since October 1973) and films taken exclusively on cine film.

A left ventricular angiogram is first made in the right anterior oblique position after the injection of 40 to 50 ml Conray 420 at 10 ml/s, using a Medrad injector. Selective coronary injections are made using hand injections with individually filled syringes containing 10 ml urografin 76 per cent.

Usually 3 injections are made into the left coronary artery, with the patient in the right then left anterior oblique and then left lateral positions. Two views are taken of the right coronary artery, the left and right obliques. The degree of rotation is adjusted individually so that the heart shadow is clear of the spine.

Pressure monitoring from the catheter tip is continuously displayed during the investigation as well as the electrocardiogram. Pacing electrodes are not inserted before coronary angiography and have never been required. Whole body anticoagulation with heparin was used routinely for about 6 months, in approximately half the cases in 1974, but this has been abandoned because there was no obvious advantage and extra danger of bleeding during and after the procedure was apparent.

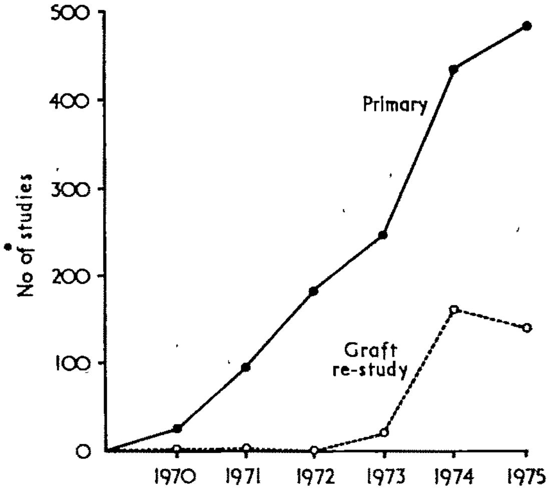

FIG. 2 *Incidence of restudies by years.*

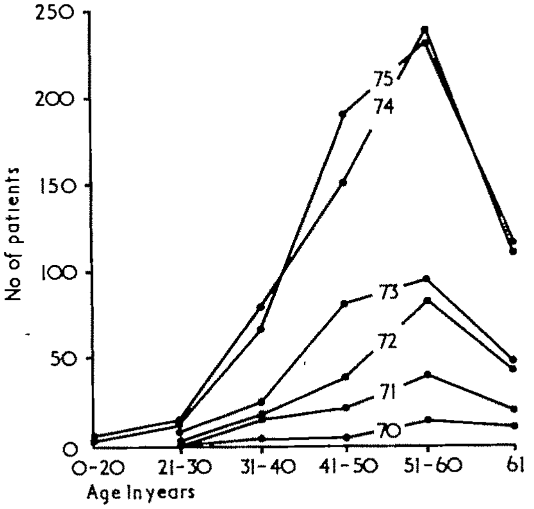

FIG. 3 *Age distribution each year.*

## Mortality

Throughout the series there have been 7 deaths occurring with 36 hours of investigation. Up to the end of 1973 there were 5 deaths resulting from 400 coronary angiograms (1·2%). In the 2 years (1974 and 1975) 2 deaths occurred in 1064 coronary angiograms (0·19%). The first 4 patients who died all had severe coronary artery disease, with poorly functioning ventricles. One patient had a ventricular aneurysm. Only one patient arrested on the table. He was immediately transferred to the theatre and cardiopulmonary bypass was instituted within 20 minutes. When the coronary arteries were opened back bleeding was seen with no sign of coronary embolism. The ventricle which showed patchy fibrosis and evidence of diffuse ischaemic damage, failed to take over and the patient died. At necropsy there was no sign of coronary dissection or other catheter trauma.

The interval between angiography and death, in the others, has been between 2 and 35 hours after returning to the ward. The last 3 deaths occurred in patients who were being investigated for crescendo angina. They had been admitted with rest pain which was not relieved by medical treatment. Coronary angiography was undertaken with a view to emergency coronary grafting. In no case did the necropsy show any evidence of recent damage to a coronary artery. Such patients are not now investigated until after an intra-aortic balloon has been introduced and counterpulsation started. Since starting this regimen no further death has occurred.

## Morbidity

Cardiac infarction, the most expected complication of coronary angiography, did not occur in any of the series.

The most important lesion resulting from coronary angiography was cerebral embolus. This occurred in 12 patients. Six of these were in the first 400 and six in the next 1000. All but 2 cleared completely—one has a mild hemiplegia and one a weakness of one leg. Two patients developed pulmonary oedema on the table and recovered with treatment. Two patients developed urticarial rashes. Fourteen patients in the first 400 suffered a severe drop in blood pressure but only 8 in the next 1000. Six patients had femoral artery problems. In one the tip of a guide wire broke off in the groin and had to be removed surgically. Four patients suffered femoral artery occlusions requiring disobliteration by a surgeon using a Fogarty catheter. One of these patients had had an obvious fall in blood pressure after left ventricular angiography which showed a large, poorly contracting chamber. Further deterioration occurred after embolectomy. Death occurred within 36 hours of the examination. One patient had severe prolonged haemorrhage. Twenty-five examinations were terminated prematurely (1·7%). Seven because of angina; 5 for persistent electrocardiographic abnormalities; 2 because of pulmonary oedema; 3 after cardiac arrest; 5 because of blood pressure drop; and 3 after embolus. Only 4 of these abandoned investigations were in the last 1000; 2 after a cardiac arrest; 1 because of persistent electrocardiographic abnormalities; and 1 because of a continuing fall in blood pressure. No permanent sequelae resulted from any of these events, other than the patient with the low blood pressure who subsequently died. Failure to pass the catheter into the aorta occurred in 21. This showed little change between 1970 and 1975. Failure to catheterize either the right or left coronary artery dropped abruptly from 16 and 20 per cent in 1970 to 3·8 and 2·7 per cent in 1972 and then gradually to 0·9 per cent and nil in 1975 (Fig. 4). In the last 1000 examinations, the failure rate for catheterization of the aorta was 1·4 per cent, the left coronary artery 0·6 per cent, and the right coronary artery 2·4 per cent. Thus successful catheterization of both coronary arteries was achieved in 95·6 per cent.

## Discussion

The data on which Petch *et al.* (1973) and Adams *et al.* (1973) based their conclusions that Sones'

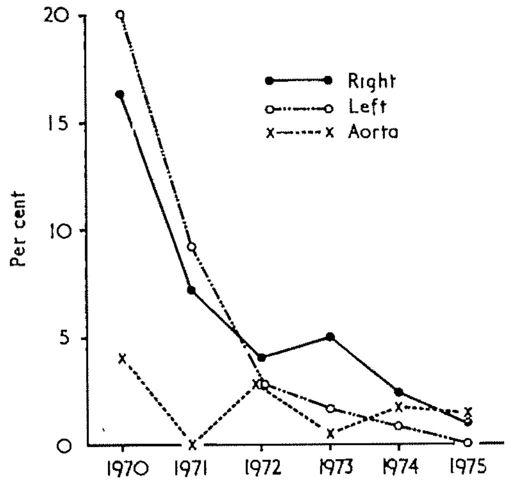

FIG. 4 *Failure to enter individual vessels expressed as a percentage of the number attempted each year.*

method of coronary angiography is safer than Judkins' are open to a different interpretation. In Adams' series, the centre doing the most femoral coronary angiograms completed 1183 in the two years with a single death. The centre doing approximately the same number of brachial aortic angiograms (1437) also had one death. The mortality rate of these two groups is not significantly different (0·08% and 0·06%). Fifty-six hospitals in this series did less than 50 angiograms each by the femoral route in the 2 years with a mortality of 2·4 per cent but the highest mortality rate of any group of hospitals undertaking Sones' method was 0·5 per cent. Sones' method requires the performance of brachial arteriotomy. This will tend to be undertaken only by trained operators.

Seldinger's technique does not require any such obvious expertise and, in consequence, is frequently attempted by the relatively inexperienced and untrained. Difference in operator ability could also have determined the method used in the National Heart Hospital series (Petch *et al.*, 1973). The fall in the mortality rate between our first 400 and the next 1000 confirms the importance of training and experience. It has been our recent practice to have a trainee operator assisted by one who is fully trained until the learner has become entirely competent. The supervising instructors must be gowned and gloved ready for action, should the learner have difficulty. Difficulty includes delay in entering either artery. The improvement in the complication rate has paralleled the reduction in time taken for each examination. Mean screening times for investigations do not reflect the increase in speed which has been acquired over the years because of the larger numbers of patients being restudied after surgery recently (Fig. 2). These may involve entering up to 4 grafts and even (occasionally) searching for one that has blocked, in addition to catheterization of the native vessels and a left ventricular angiogram.

Although the cases which are now subjected to coronary angiography include patients who are less seriously ill than formerly, the lower complication rate cannot only be a reflection of the lesser severity of the coronary disease, though this must be important. In 1975 the lumen of more than two-thirds of all vessels catheterized was reduced to less than half its original size. Of the last 1000 studies, 564 were on patients who had later (or previously) had a cardiac operation. A further 13·2 per cent had ventricular functions too poor for operations to be undertaken or were primary cardiomyopathies. Only 4 per cent had normal studies. The 264 not operated on include some who are still on the waiting list for operation. The low incidence of complications associated with the Seldinger procedure is attributed to careful attention following the original instructions (1953). That is, when possible, only the anterior wall of the artery is punctured and the needle inserted sufficiently low that should the back wall be transfixed, the rear hole is below the inguinal ligament and capable of occlusion by compression. Most important, no force must be used in the passage of the catheters which should flow smoothly and easily. A normal arterial pressure must be recorded at all times other than during actual injections. Should the pressure drop, the catheter must be withdrawn from coronary or femoral artery immediately—even though there may have been difficulty in entering the artery.

## Conclusion

Coronary angiography by Judkins' technique is a safe procedure when performed by experienced operators. Operators should not be in charge of coronary catheterization until they have proved themselves to be competent during a period of close supervision. During this period of supervision a completely competent operator should be acting as assistant and prepared to take over should the need arise. Taking over from the learner should not be delayed but should occur at the first hint of difficulty. Units would no longer be justified in starting coronary angiography unless they have a fully experienced person in charge. One would expect such a person to have at least 2 years' experience of coronary angiography and a minimum of 200 angiograms to their credit.

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# Antilipolytic therapy in angina pectoris
## *Reduction of exercise-induced ST segment depression*

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*A double-blind cross-over study was performed on 12 men with stable angina pectoris in order to determine the effect of antilipolytic treatment on exercise tolerance and exercise-induced electrocardiographic changes. The men were exercised to the onset of anginal pain using a reproducible and standardized ergometric load.*

*A nicotinic acid analogue was used to reduce plasma free fatty acids and free glycerol before and during exercise testing and to eliminate their post-exercise rise. This was associated with significant reduction of exercise-induced ST segment depression ($P<0{\cdot}005$), though there was no significant difference in the duration of exercise before the onset of pain.*

*A change in the proportions of lipid and carbohydrate for oxidation by the ischaemic myocardium, making relatively more glucose available, is a likely explanation.*

The availability of free fatty acids (FFA) to the myocardium is increased during physical activity because of augmented intramyocardial lipolysis (Kaijser *et al.*, 1972) and also because of a rapid rise in plasma concentration caused by continued mobilization from adipose tissue (Friedberg *et al.*, 1960; Carlson, 1967). These changes are likely to be more pronounced in patients with ischaemic heart disease than in healthy subjects, since the former have an excessive accumulation of intramyocardial lipid (Wartman *et al.*, 1956) and frequently show an exaggerated lipolytic response to adrenergic stimulation (Kershbaum *et al.*, 1961; Penick, 1962). Such observations have suggested that control of the metabolic response to exercise may be of value to patients with angina pectoris, since there is biochemical (Kurien and Oliver, 1970; Shug and Shrago, 1973; de Leiris, Bricknell, and Opie, 1974), experimental (Kurien, Yates, and Oliver, 1971; Kjekshus and Mjøs, 1972; 1973), and clinical (Oliver, Kurien, and Greenwood, 1968; Rowe, Neilson, and Oliver, 1975) evidence that excess FFA can be harmful during myocardial ischaemia.

This might be achieved either by antilipolytic treatment or by increasing glucose availability (Oliver, 1972; Opie, 1972). Lipolysis in adipose tissue and in the heart is inhibited by nicotinic acid (Carlson and Orö, 1962; Christian *et al.*, 1969; Lassers *et al.*, 1972), but it can have a distinct hypotensive effect. A nicotinic acid analogue (NAA), 5-fluoro-3-hydroxy-methylpyridine hydrochloride, produces few haemodynamic effects but retains a potent antilipolytic action (Rowe *et al.*, 1973). This report describes the effects of this drug on exercise tolerance and exercise-induced electrocardiographic changes in patients with stable angina.

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## Patients and methods

### Patients

Twelve men aged 49 to 65 years (average 56 years) were studied. All had angina pectoris for a minimum of 6 months before the study: the average duration from onset of symptoms was 70 months (range 9 months to 10 years). Three of these men had an inferior myocardial infarct more than 6 months before and had residual electrocardiographic abnormalities at rest; 8 developed horizontal or downsloping ST segment depression of 1 mm in response to exercise; and 1 patient without electrocardiographic evidence of myocardial ischaemia had severe three-vessel disease shown by coronary angiography.

Eight patients had been taking a beta-adrenergic blocking drug: the dosage was halved 10 days before and stopped 72 hours before the study. All lipid lowering agents were discontinued 4 weeks before entering hospital. No patient was taking a digitalis preparation or diuretic and all were free of clinical evidence of left ventricular failure. Four patients were cigarette smokers but this was not allowed while they were in hospital. Body weight averaged 75 kg (range 65 to 90 kg).

### Clinical and laboratory procedures

The patients were admitted to hospital for 3 days. Preliminary studies were performed on the first day, when exercise tests were done to establish a 'pain work load' (i.e. the work load necessary to induce pain in each individual), to familiarize the patient with the equipment, and to minimize the problem of improvement in exercise tolerance with successive tests. The exercise was performed using a constant load, upright bicycle ergometer (Elema Ergometer System 380). Continuous electrocardiographic monitoring was performed from bipolar chest leads CR2, CR4, and CR5 during exercise, and standard leads I, II, III and orthodox chest leads V2, V4, and V5 after exercise. The electrocardiogram was recorded with an Elema Mingograf 34 ink-writing machine at standard calibration (10 mm = 1 mV) and measurement made with paper speed 25 mm/s.

A well-tried exercise procedure was followed (Redwood *et al.*, 1971): on day 1 the work load was started at 200 kilopond metres per minute (kpm/min) and increased by 100 kpm/min each minute until pain occurred (i.e. 'pain work load'). The subject was rested for 20 minutes and the study repeated starting at the 'pain work load' minus 100 kpm/min, with an increase by 100 kpm/min each 3 minutes. This was designed to produce pain within the second 3-minute period, which is the optimum time for assessment of antianginal agents (Reichek *et al.*, 1974).

On days 2 and 3, the exercise study was performed in the morning after an overnight fast. A cannula was inserted into an antecubital vein under local anaesthesia 75 minutes before starting exercise and the patients remained supine. After 15 minutes either 100 mg NAA or 10 ml normal saline were administered intravenously over 5 minutes. The administration of drug or placebo on days 2 or 3 was randomly determined and the study was conducted double blind. Exercise was begun at the 'pain work load' minus 100 kpm/min. This was increased by 100 kpm/min every 3 minutes, and the time from establishing the first constant work load to the onset of pain was measured to the nearest second by a stopwatch. After exercise the patient rested for 20 minutes. Blood, 20 ml, was drawn for serum FFA (Trout, Estes, and Friedberg, 1960) and glycerol (Chernick, 1969) concentrations at –75 min, –60 min (before injection), –30 min, and immediately before exercise; at the onset of pain; and 20 minutes later. Plasma glucose (Nimmo, Kirby, and Lassers, 1973) was estimated at –60 min before exercise and at the onset of pain.

Systolic and diastolic pressures were measured at each of the above intervals by a mercury manometer and cuff using phase 4 of Korotkov for the diastolic pressure. Heart rate was measured from electrocardiograms at the same time, and also at 1-minute intervals for 8 minutes after the onset of pain.

Exercise-induced ST segment depression was measured 'blind' by the same observer at intervals of 1 minute after the onset of pain. It was recorded to the nearest 0·5 mm at the point of maximum depression in horizontal or downsloping segments, or at the point of the minimum depression in upsloping segments. The sum of the ST depression from leads I, II, III and V2, V4, and V5 at each minute was used as the index of ST change for each patient.

Changes in ST segments at each interval were compared using the Wilcoxon test for non-parametric data. The combined results, over all the time periods, were analysed using Friedman's method of analysis of variance of ranked data (Colquhoun, 1971). Other statistical analyses were by Student's t-test (two-tailed).

## Results

### Metabolic changes

The changes in plasma FFA and plasma glycerol are summarized in Fig. 1. There was no significant difference between FFA and glycerol concentrations before the injection of NAA or placebo on the 2 successive days of the study. The downward trend with time was related to the period of rest (Carlson, 1967).

The changes in response to exercise on the placebo day were similar to those previously reported in healthy subjects (Carlson, 1967; Friedberg *et al.*, 1960). After administration of the NAA, the plasma FFA and glycerol levels were at all times significantly below those recorded on the placebo day. In particular, plasma FFA and glycerol were below the initial levels immediately after stopping exercise and the normal post-exercise rebound rise in FFA was almost completely abolished by the NAA.

The mean plasma glucose at the time of pain on the placebo day was 5·2 ±0·3 mm/l (93 ±6 mg/100 ml) (±SEM) and on the NAA day 5·5 ±0·3 mm/l (99 ±5 mg/100 ml) (NS).

## Exercise tolerance

The period for which patients exercised before the onset of pain on the 2 days (NAA and placebo) was not significantly different (Fig. 2). The mean duration of exercise over the placebo day was 4 min, 32 s ±47 s (±SEM) and on the NAA day was 4 min, 14 s ±40 s (NS).

## Electrocardiographic changes

There was no significant difference in ST segment depression in each patient's electrocardiogram before the administration of drug or placebo on the 2 days of the study. The NAA produced significantly less ST segment depression during the 8 minutes immediately following the completion of exercise (Table). The overall difference between drug and placebo was highly significant ($P < 0·005$).

No patients developed arrhythmias on either day of the study except for single ventricular premature beats. Seven patients had one or more ventricular premature beats during exercise and the 8 minutes after pain. The mean number of ventricular premature beats recorded during the exercise and post-exercise period of the placebo day was 1·8 (range 0 to 15) and on the NAA day 3·0 (range 0 to 26) (NS).

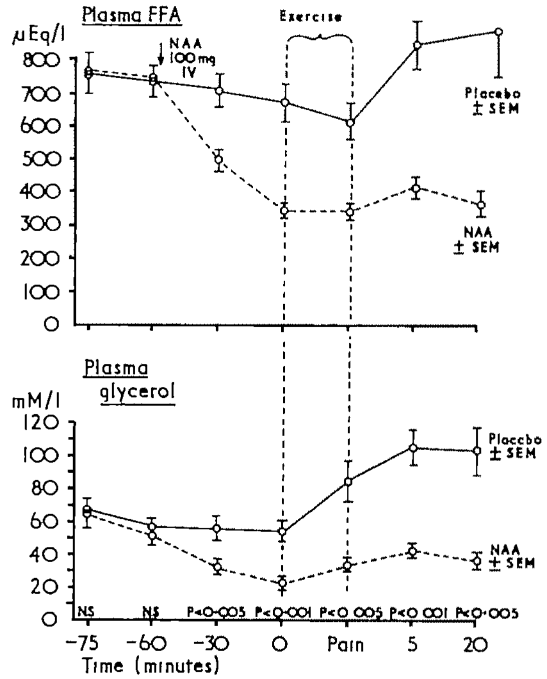

FIG. 1 *Plasma FFA (upper graph) and plasma glycerol (lower graph) in 12 men with angina when receiving placebo or the nicotinic acid analogue (NAA).*

## Haemodynamic changes

There was no significant difference in each patient's heart rate or systolic and diastolic blood pressure in the period before exercise on either day. The average heart rate for the 12 patients on the NAA day was slightly lower at all times from the onset of pain and this reached statistical significance at the onset of pain (placebo 120±7 beats per min: NAA 112±6 beats per min: $P < 0·03$) and at 3

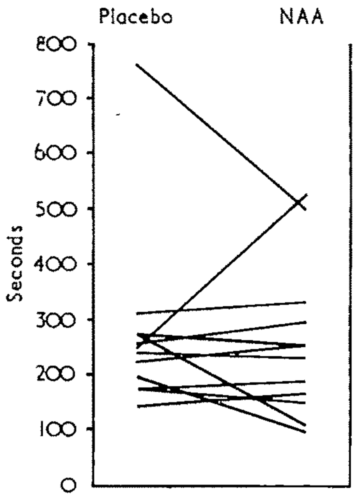

FIG. 2 *Duration of exercise before the onset of pain when receiving a placebo (to the left of the figure) and the nicotinic acid analogue (to the right of the figure) in 12 men with angina. The results for each man are connected.*

TABLE *Effect of nicotinic acid analogue on ST segment depression after exercise in 12 men with angina pectoris, who acted as their own controls*

| | *ST segment depression mean ± SEM (mm)* | | |
|---|---|---|---|
| *Minutes after exercise* | *Placebo* | *Nicotinic acid analogue* | *P (analysis of paired data n=12)* |
| 1 | 1·8±0·5 | 0·9±0·4 | <0·025 |
| 2 | 2·0±0·8 | 1·2±0·6 | <0·025 |
| 3 | 1·8±0·7 | 1·5±0·6 | NS |
| 4 | 1·7±0·7 | 1·2±0·5 | NS |
| 5 | 1·4±0·5 | 0·9±0·4 | <0·025 |
| 6 | 1·2±0·8 | 0·6±0·4 | <0·025 |
| 7 | 1·1±0·5 | 0·5±0·3 | NS |
| 8 | 0·8±0·5 | 0·4±0·3 | NS |
| Combined difference | | | <0·005 |
| Pre-exercise | 0·3±0·2 | 0·3±0·1 | NS |

minutes after pain (placebo 76 ±5 beats per min: NAA 68 ±4 beats per min : $P < 0.02$). On the day of the NAA, there was a trend for the systolic blood pressure to be higher when pain occurred (placebo 160 ±6 mmHg (21·3 ±0·8 kPa) : NAA 177 ±8 mmHg (23·5 ±1·1kPa) : $P = 0.10$) and for the diastolic blood pressure to be higher at 5 minutes after pain (placebo 91 ±2 mmHg (12·1 ± 0·3kPa) : NAA 96 ± 2 mmHg (12·8 ±0·3kPa) : $P < 0.025$). The product of systolic blood pressure and heart rate was not significantly different for all patients either before exercise, at the point of pain, or 5 minutes after pain.

## Discussion

Depression of the ST segment induced by standardized exercise in patients with angina was less when they were given a nicotinic acid analogue (NAA). A metabolic explanation is likely, since this NAA decreased plasma FFA before exercise and reduced the expected postexercise rise, presumably leading to decreased FFA extraction by the myocardium (Carlson *et al.,* 1972). As the NAA has an antilipolytic effect similar to nicotinic acid, reduction in any exercise-induced increase in myocardial lipolysis (Lassers *et al.,* 1972) may also have occurred. Reduction of FFA extraction will change the proportion of lipid and carbohydrate making relatively more glucose available for oxidation by the myocardium. Similar findings have been reported recently during infusion of glucose-insulin-potassium in atrial-pacing-induced angina (Chiong, West, and Parker, 1976). Reduction of intracellular FFA could lead to an increase in available ATP (Shug and Shrago, 1973), stabilize membrane function (Pande and Mead, 1968), and decrease myocardial oxygen consumption (Mjøs, 1971) and all these would reduce the effects of myocardial ischaemia at a given work load. A metabolic explanation is also supported by the positive correlation between the degree of ST segment depression and coronary sinus lactate levels, measured during atrial pacing in patients with ischaemic heart disease (Parker *et al.,* 1969): this correlation persisted into the recovery phase after the cessation of pain, unlike changes in haemodynamic parameters of myocardial oxygen consumption which correlate poorly with ST changes after exercise (Detry, Piette, and Brasseur, 1970). The possibility also arises that this nicotinic acid analogue has a direct effect on intracellular potentials, independent of its antilipolytic action, but nicotinic acid itself has recently been shown not to have any such effect on mammalian ventricular muscle fibres (Beresewicz and Wojtczak, 1976).

The haemodynamic changes at the time of pain could be explained by increased myocardial contractility with a rise in blood pressure and reflex decrease in heart rate. An increase in contractility produced by a reduction in FFA levels has been shown in ischaemic dog hearts (Kjekshus and Mjøs, 1972). The oxygen requirements might, therefore, be determined by a complex interaction between increased metabolic efficiency and increased contractility, which results in unchanged exercise tolerance. A test of this hypothesis would require measurement of the ejection time, dP/dt, ventricular volumes, and measurement of coronary sinus indices of ischaemic metabolism, such as lactate, potassium, and creatine phosphokinase.

There was no significant difference in the time during which patients could exercise before the onset of pain. The disparity of effect of the NAA on ST segment depression and pain threshold is not explained, though it has already been recognized that the correlation of ST changes with pain is poor (Borer *et al.,* 1975). The product of systolic pressure and heart rate has been shown to correlate positively with myocardial oxygen requirements and, in a given individual, has a constant value at the onset of ischaemic chest pain (Robinson, 1967). It has also been shown that there is a close positive correlation between the degree of ST segment depression during exercise and this product. This correlation holds even if the same product reflects an increased heart rate and lower blood pressure on different occasions (Detry *et al.,* 1970). But there was no difference in this product when pain occurred on each of the 2 days of this study, despite a significant decrease in heart rate with the NAA as this was compensated by a trend towards higher blood pressure.

This is the first demonstration that reduction of plasma FFA concentration can alter ST segment changes associated with myocardial ischaemia. Though pain tolerance was unchanged, further studies of the effects of metabolic intervention in patients with angina are indicated.

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# *Case reports*

*British Heart Journal,* 1976, **38,** 1209–1212.

# Echocardiographic diagnosis of large fungal verruca attached to mitral valve

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*In a patient with endocarditis due to* Candida tropicalis *echocardiograms from mitral valve vegetations were found to mimic the typical pattern of a left atrial myxoma. A mass was shown occupying the mitral orifice posterior to the anterior mitral leaflet; densities also appeared in the left atrium. Though these echocardiographic findings were consistent with the diagnosis of a left atrial myxoma, there were other distinctive differential diagnostic features. Other diagnostic possibilities must, therefore, be considered in the interpretation of echocardiograms which suggest left atrial tumour.*

## Case report

A 63-year-old man was transferred to Yale-New Haven Hospital from a chronic care institution because of dizziness and increasing weakness of two days' duration. He had been in good health until 10 months before this transfer, when he was admitted to another hospital elsewhere, having woken with weakness of his right arm and ataxia. A grade 3/6 apical holosystolic murmur radiating to the axilla was then heard. The cerebrospinal fluid was xanthochromic; a left carotid arteriogram was normal. He was discharged after 34 days with a diagnosis of cerebrovascular accident, of unknown aetiology. Blood cultures were negative at that time.

Three months before transfer he was admitted to the urology service of the other hospital for evaluation of a left upper quadrant abdominal mass. At operation a benign renal cyst was found and oversewn. Subsequently because of persistent fatigue he entered a chronic care institution and remained there for 48 hours before the transfer to Yale-New Haven Hospital.

On examination on admission to this hospital, he was an elderly, confused man. Oral temperature was 38·5°C. He had bilateral Roth spots. There was a 3+ left ventricular heave. A grade 3/6 holosystolic murmur was heard at the cardiac apex, with radiation to the axilla, but there was no diastolic murmur. There was bilateral facial paresis and a flaccid right hemiplegia. Laboratory data included a haematocrit of 31 per cent and a white blood count of 6400 cells/mm$^3$ with a shift to the left. CSF was again xanthochromic. Brain scan and skull *x*-ray films were normal. Chest *x*-ray film showed slight cardiomegaly, without evidence of left atrial enlargement, and clear lung fields. The electrocardiogram showed left anterior hemiblock and left atrial enlargement. Fig. 1 shows the echocardiogram obtained using standard techniques[1] (Popp *et al.*, 1969), with the transducer in the usual position for examination of the mitral valve. Towards the left of the figure abnormal densities appear posterior to the anterior mitral leaflet. Prolapse of the anterior or posterior leaflet is suggested throughout and is most clearly seen on the right hand side of Fig. 1. Fig. 2 is a scan from the aortic to the mitral region showing an irregular left atrial density during the latter half of diastole, disappearing shortly after the onset of the systole. Dense echoes are seen in the mitral orifice during diastole.

Blood cultures on admission grew *Candida tropicalis*. The patient was treated with amphotericin-B (50 mg daily); his condition remained stable until one week after admission when he had

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[1] Unirad Series C Ultrasonoscope, Unirad Corp., Denver, Colorado.

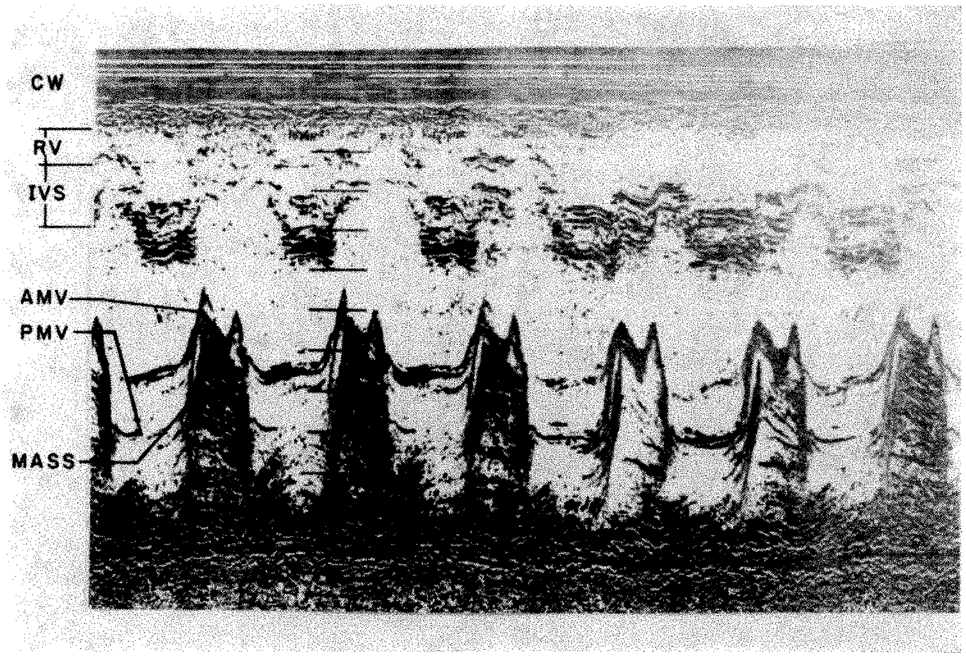

FIG. 1 *Echocardiogram in normal mitral position. The normal anterior mitral leaflet (AMV) appears thin; the 'a' wave is prominent. The posterior mitral leaflet (PMV) is obscured by the mass during diastole. On the left side of the figure, dense echoes filling the mitral orifice during diastole appear, but are not seen during systole in this view. While these dense echoes did not disappear with reduction in gain, they became less prominent with slight transducer movement as seen in the right of the figure.*

*The exact origin of the structure labelled PMV in this illustration is controversial. Though we have regarded this as posterior mitral leaflet, it is possible that a structure resembling this might in fact represent a severely prolapsing leaflet or both leaflets together (Popp* et al., *1974).*

*AMV—anterior mitral valve leaflet; CW—chest wall; IVS—interventricular septum; PMV—posterior mitral valve leaflet; RV—right ventricle.*

further emboli with impaired consciousness, left hemiparesis, and absent pulses in the left leg. A left femoral embolectomy was performed and microscopical examination of the embolus showed thrombus and fungal forms.

On the following day, at cardiac catheterization, an angiocardiogram following injection into the pulmonary artery showed a spherical filling defect behind the mitral valve, moving with the posterior leaflet; there was significant prolapse of the posterior leaflet into the atrium during systole and the leaflet appeared thickened and nodular.

At operation next day, a large fungal mass was found to be attached to the posterior mitral valve leaflet. The mitral valve was excised and a Starr-Edwards prosthesis was implanted. The operative specimen consisted of calcified and fibrous valve tissue with large, irregular, fibrinous vegetations easurinmg 2 cm at the greatest diameter. Histologically, masses of fungal organisms contained in a thrombotic mesh were seen. No myxomatous tissue was present.

Fever persisted and, after a protracted course complicated by respiratory and renal failure, he died on the 20th postoperative day.

## Discussion

The occurrence of fungal endocarditis with the development of large fungal vegetations attached to the mitral or aortic valve is becoming increasingly common (Drutz, 1971). Once candida was grown from the blood cultures there was little doubt, on clinical grounds, that our patient had fungal endocarditis. The echocardiogram was, however, obtained before cultures became positive and

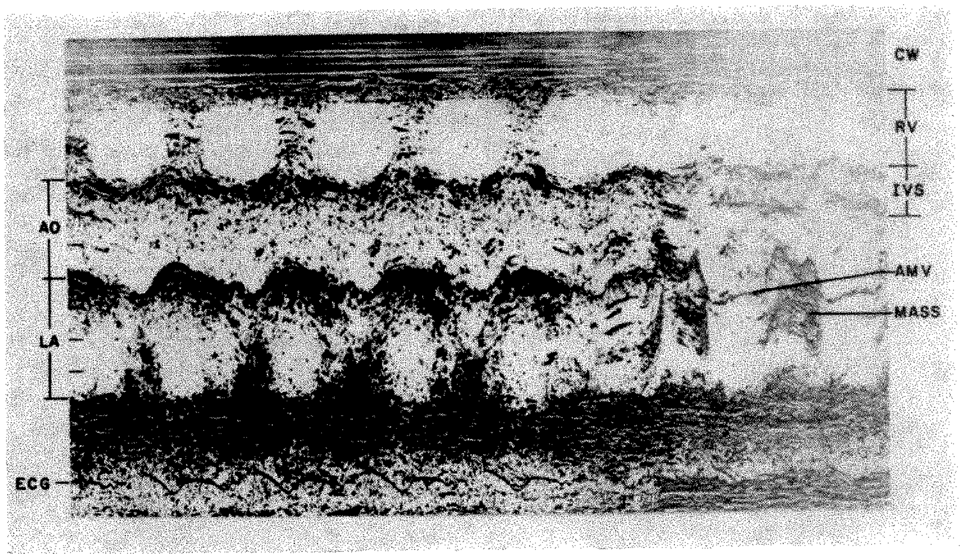

FIG. 2 *Echocardiographic scan of aortic and mitral regions. The mass is posterior to the anterior leaflet (AMV) during diastole. Echocardiographic densities are shown in the left atrium (LA) during late diastole and early systole. AMV—anterior mitral valve leaflet; AO—aortic root; CW—chest wall; ECG—electrocardiogram; IVS—interventricular septum; LA—left atrium; RV—Right ventricle.*

the question of left atrial myxoma was raised. It is understandable that a fungal verruca on the mitral valve should mimic a left atrial myxoma echocardiographically, in view of their similar size and site. When positive blood cultures were obtained the possibility of an infected myxoma was considered. Though rare, such cases have been reported (Dick and Mullin, 1956), with candida as the infecting organism.

Dillon and his colleagues have reported on the echocardiographic findings in 8 patients with bacterial endocarditis (Dillon *et al.*, 1973). In all cases vegetations were between 2 and 8 mm in size, and thus were much smaller than the lesion reported in our patient (2 cm at greatest diameter). The typical manifestations included apparent valvular thickening with a 'shaggy appearance'. The initial diagnostic uncertainty in this case resulted from the echocardiograms illustrated in Fig. 1 and 2. The authors of recent echocardiographic study of left atrial myxoma have observed that 'the recording of abnormal echoes from the region posterior to the anterior leaflet of the mitral valve during ventricular diastole is one of the most reliable manifestations of a tumour' (Martinez, Giles, and Burch, 1974). In addition, in a recent published report such a pattern is described as 'pathognomonic' of the condition (Case Records of the Massachusetts General Hospital, 1973). Dillon *et al.* (1973) have discussed the differentiating features between a myxoma and endocarditis. With tumour the posterior leaflet is not seen, the extra echoes appear to be unattached to the valve leaflet, and finally the tumour can frequently be seen as multiple irregular echoes in the left atrium. Though abnormal multiple echoes appear in the left atrium of our case, their timing (late diastole and early systole) is inconsistent with the usual myxoma pattern. Thus, this case shows that the demonstration of an abnormal mass posterior to the anterior mitral leaflet is insufficient evidence on which to make the diagnosis of left atrial myxoma.

Our experience with this case confirms that caution must be exercised in the interpretation of echocardiograms thought to show a left atrial myxoma. Other diagnoses, including bacterial and fungal endocarditis, must be considered. Echocardiography, however, is still a valuable screening investigation in patients with suspected lesions of the mitral valve. With the experience of cases such as the one reported here the range of conditions recognized by echocardiography widens further. Moreover, serial echocardiograms may be useful when such patients are treated medically; it may then be possible to observe repression of vegetations in endocarditis.

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# Left ventricle to pulmonary artery conduit in treatment of transposition of great arteries, restrictive ventricular septal defect, and acquired pulmonary atresia[1]

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*Progressive cyanosis after banding of the pulmonary artery in infancy occurred in a child with transposition of the great arteries and a ventricular septal defect, and a Blalock-Taussig shunt operation had to be performed. At the time of correction a segment of pulmonary artery between the left ventricle and the band was found to be completely occluded so that continuity between the left ventricle and the pulmonary artery could not be restored. A Rastelli type of operation was not feasible as the ventricular septal defect was sited low in the muscular septum. Therefore, in addition to Mustard's operation, a Dacron conduit was inserted from the left ventricle to the main pulmonary artery to relieve the obstruction. Postoperative cardiac catheterization with angiocardiography indicated a satisfactory haemodynamic result. Tne patient remains well 11 months after the operation. This operation, a left ventricle to pulmonary artery conduit, may be used as an alternative procedure in patients with transposition of the great arteries, intact interventricular septum, and obstruction to the left ventricular outflow, if the obstruction cannot be adequately relieved.*

Infants with transposition of the great arteries and ventricular septal defect may be treated either by early closure of the ventricular septal defect and Mustard's operation or by pulmonary artery banding in infancy followed by later correction (Stark *et al.,* 1970; Neutze and Clarkson, 1973; Stark, 1973; Subramanian, 1973; Trusler and Mustard, 1974).

An unusual complication of pulmonary artery banding occurred in a child with transposition of the great arteries plus ventricular septal defect who had had the pulmonary artery banded in infancy. Subsequently a Blalock-Taussig anastomosis had been performed because of increasing cyanosis. A segment of pulmonary artery between the left ventricle and the band had become completely occluded, so that at the time of correction continuity between the left ventricle and pulmonary artery could not be restored. A Rastelli type of operation was not feasible because the ventricular septal defect was small and located in the lower part of the muscular septum. Therefore, in addition to Mustard's operation, a Dacron conduit was inserted from the left ventricle to the main pulmonary artery to relieve the obstruction.

## Case report

This male infant was the product of a normal pregnancy and delivery and weighed 3·3 kg at birth. Cyanosis was present from birth and he suffered recurrent chest infections and failed to gain weight in the early months of life. Examination showed a moderate degree of cyanosis with a harsh systolic murmur along the left sternal border. Chest *x*-ray examination showed an enlarged heart and pulmonary plethora. The infant was digitalized and cardiac catheterization with angiocardiography were undertaken at the age of 25 days. A diagnosis of transposition of the great arteries, ventricular septal defect, and pulmonary hypertension (Table 1) was made. Attempted balloon atrial septostomy was unsuccessful. Recurrent chest infections and congestive cardiac failure prevented his discharge home and at the age of 10 months he was referred to this unit. Examination revealed a small, cyanosed infant with digital clubbing, tachypnoea, and tachycardia. A systolic murmur was heard over the praecordium. The liver was enlarged 3 cm below

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TABLE 1 *Catheterization data*

| *Site* | *3 weeks* | *10 months* | *10 months (after Blalock-Hanlon procedure)* | *2 years* | *6½ years (patent Blalock-Taussig shunt)* |
|---|---|---|---|---|---|
| *Pressures (mmHg)* | | | | | |
| Right atrium (mean) | | 7 | 0 | 4 | 5 |
| Right ventricle | 55/5 | 84/2–12 | 80/3 | 100/6 | 110/4 |
| Aorta | 55/18 | 88/64 | 80/44 | 96/66 | 110/50 |
| Left atrium (mean) | | 10 | 0 | 5 | 4 |
| Left ventricle | 48/0 | 80/0–9 | 70/5 | 120/20 | 240/2 |
| Main pulmonary artery | 48/24 | 60/30 | 70/28 | 120/20 | Not entered |
| Pulmonary artery distal to band | | | | 12/10* | 20/16† |
| *$O_2$ saturation (%)* | | | | | |
| Aorta | 33 | 44 | 74 | 47 | 85 |

*Right pulmonary artery.
†Via Blalock-Taussig anastomosis.
*Conversion from Traditional to SI Units:* 1 mmHg≈0·133 kPa.

the costal margin. The electrocardiogram showed right ventricular hypertrophy and the chest *x*-ray film showed an enlarged heart with pulmonary plethora. Haemoglobin was 15 g/dl.

Further cardiac catheterization confirmed the diagnosis of transposition of the great arteries and ventricular spetal defect. The aortic oxygen saturation was 44 per cent; A Blalock-Hanlon procedure was therefore performed, and the arterial oxygen saturation rose to 74 per cent. As he remained in congestive cardiac failure another cardiac catheterization was performed two weeks later which confirmed that a high pulmonary flow was present with a high pulmonary artery pressure (Table 1). The pulmonary artery was, therefore, banded. After this he improved and was discharged from hospital on a maintenance dose of digoxin. During the next year his general condition improved.

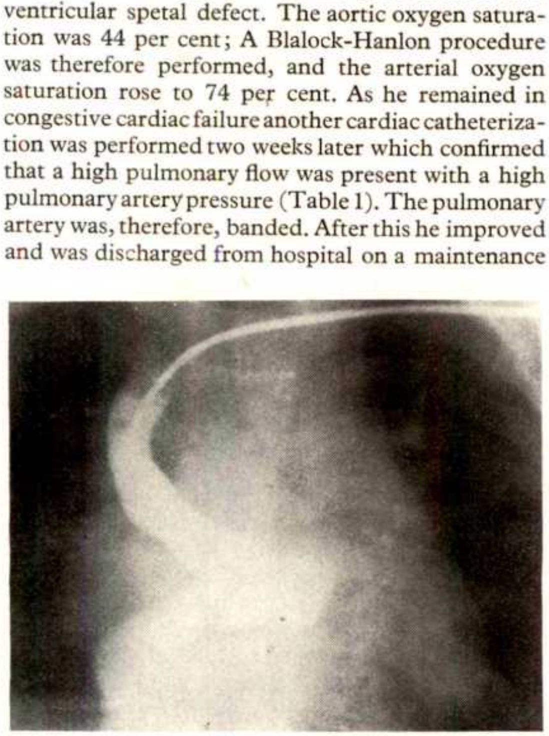


FIG. 1 *Angiogram after injection into superior vena cava. Systemic venous atrium and superior and inferior venae cavae are opacified.*

He was readmitted at the age of 2 years because of sudden deterioration. At this time central cyanosis with clubbing was increased and the systolic murmur was still audible over the left sternal border. The liver was enlarged 4 cm below the costal margin. The haemoglobin was now 22 g/dl. His general condition indicated a low cardiac output. Repeat cardiac catheterization (Table 1) showed an aortic saturation of 47 per cent.

A right Blalock-Taussig shunt was subsequently performed. Cyanosis decreased and the aortic saturation rose to 78 per cent. He was seen regularly in the follow-up clinic and remained well and active with a good exercise tolerance.

At the age of 6½ years he was admitted electively for reinvestigation with a view to correction. Examination revealed mild cyanosis and clubbing. There was biventricular hypertrophy with a thrill and grade 4/6 pansystolic murmur along the left sternal border. The haemoglobin was 16 g/dl. Cardiac catherization with angiography showed transposition of great arteries with a minimal left-to-right shunt through a low, muscular ventricular septal defect. The pulmonary artery filled only through the patent Blalock-Taussig anastomosis (Table 1).

The operation was performed at the age of 6 years and 11 months, using cardiopulmonary bypass. The right Blalock-Taussig shunt was ligated. While the pulmonary artery was being dissected, the right coronary artery was inadvertently opened because of dense adhesions and then repaired with 6–0 Prolene. The segment of pulmonary artery between the band and pulmonary valve was fibrosed and completely occluded. The left ventricle was

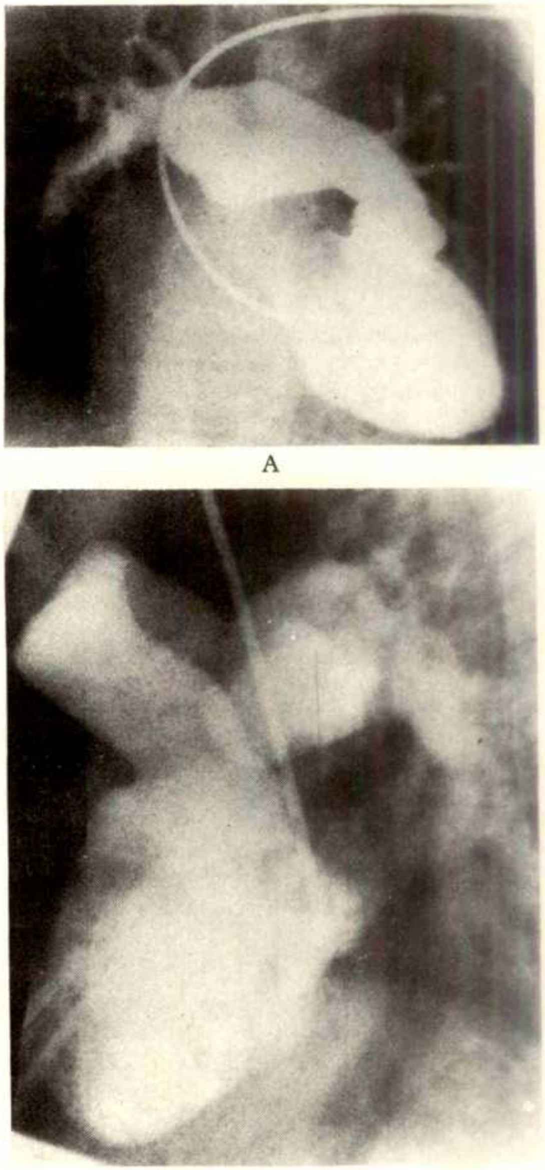
TABLE 2 *Postoperative catheterization*

| | *Pressure (mmHg)* | $O_2$ *Saturation* (%) |
|---|---|---|
| Superior vena cava | 8 (mean) | 72 |
| Inferior vena cava | 8 (mean) | 70 |
| Systemic venous atrium | a=10 v=10<br>x=8 y=−2 | — |
| Left ventricle | 75/4–6 | 73 |
| Pulmonary artery | 35/5 | 72 |
| Left pulmonary artery (wedge) | a=9 v=14<br>x=6 y= 8 | — |
| Pulmonary venous atrium | a=8 v=16<br>x=0 y= 0 | 95 |
| Right ventricle | 115/4–8 | — |
| Aorta | 115/65 | 94 |

*Conversion from Traditional to SI Units:* 1 mmHg≈0·133 kPa.

then opened to visualize the left ventricular outflow tract. There was no outlet from the left ventricle to the pulmonary artery. As neither a Hancock prosthesis nor an aortic homograft was available a No. 20 valveless Dacron tube was sutured to the left ventriculotomy site between branches of coronary arteries and connected to the distal end of the main pulmonary artery, using a 4–0 Prolene running stitch. A standard Mustard procedure was then performed using a pericardial patch. The ventricular septal defect was left open to act as a vent for the hypertrophied left ventricle in case the conduit became partly obstructed. The patient came off bypass without difficulty, haemostasis was achieved, and the chest was closed in a routine manner. After the operation he was ventilated and the circulation was maintained with minimal support from inotropic agents. He was given digitalis and the other inotropic agents were discontinued 72 hours later. He was extubated on the fifth postoperative day. Diuretics were given because of fluid retention. He remained well and was discharged 3 weeks after operation.

The child was readmitted for evaluation, including cardiac catheterization, 4 months later. He was pink and his exercise tolerance was much improved. He was taking digoxin only. A grade 4/6 systolic murmur was audible over the praecordium and the liver edge was felt 2 cm below the costal margin. The lungs were normal. Haemoglobin was 13 g/dl. The electrocardiogram showed sinus rhythm with right ventricular hypertrophy. The results of cardiac catheterization are shown on Table 2. No intracardiac shunt was detected at atrial or ventricular level, the superior and inferior venous pathways were unobstructed (Fig. 1) and the patency of the right coronary artery was confirmed. The conduit which leads from the left ventricle to the main pulmonary artery was patent, with mild to moderate regurgitation (Fig. 2). The left ventricle ejected almost all the regurgitant portion of contrast material early in the subsequent systole. Both ventricles showed a normal pattern of contraction over the angiocardiogram.



A

B

FIG. 2 *Left ventricular angiocardiogram. A) Anteroposterior projection; left ventricle, conduit, and main pulmonary artery are shown. B) Lateral view. Note that the conduit is placed in front of the ascending aorta.*

At present, 11 months after the operation the child remains well. He is fully active and on no medication. The heart is still slightly enlarged and a 3/6 systolic murmur can be heard over the praecordium.

## Discussion

Occlusion of the main pulmonary artery is a rare complication after banding of the pulmonary artery (Dobell *et al.,* 1973). In our patient the pulmonary valve and the main pulmonary artery were completely obliterated and fibrotic after the previous pulmonary artery banding.

It was impossible to repair the main pulmonary artery with a patch. The ventricular septal defect was situated low in the muscular septum and was restrictive in nature. Because of these unusual circumstances, we elected to proceed with Mustard's operation and then place a Dacron conduit from the left ventricle to the pulmonary artery. A valveless conduit was used because neither a homograft nor a heterograft valve was available.

This approach may perhaps be used in other patients. In several patients with transposition of the great arteries, intact ventricular septum, and left ventricular outflow tract obstruction, we were unable to remove the obstruction completely. This was especially so in patients with a redundant mitral valve or a long fibromuscular type of obstruction. So far these patients seem to tolerate a high left ventricular pressure with gradients of 80 to 90 mmHg (10·6 to 12·0 kPa) well. Should they deteriorate later, a left ventricular to pulmonary artery conduit seems to be a logical solution. Attempts to treat patients with transposition of the great arteries, intact ventricular septum, and left ventricular outflow tract obstruction by creating a high ventricular septal defect and performing a Rastelli operation were unsuccessful (Danielson *et al.,* 1971). A conduit from the posterior ventricle has been used recently by Bernhard, Poirier, and LaFarge (1975). They inserted a valve containing a conduit between the left ventricle and descending aorta in a patient with congenital aortic stenosis and hypoplasia of the aortic valve annulus.

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# Reversion to sinus rhythm 11 years after surgically induced heart block

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*A patient is presented in whom the heart reverted spontaneously to sinus rhythm 11 years after surgical closure of a ventricular septal defect complicated by complete heart block. It seems unlikely that regeneration of fibres in the bundle of His, if these had indeed been destroyed, could account for the restoration of sinus rhythm after so long an interval.*

The outlook for most patients with the congenital form of third degree atrioventricular block is excellent (Campbell and Emanuel, 1967), but when acquired as a complication of cardiac surgery it is usually of grave significance unless it reverts to sinus rhythm soon after operation (Fryda, Kaplan, and Helmsworth, 1971). We report a patient in whom complete heart block developed during surgical repair of a ventricular septal defect and who experienced spontaneous reversion to sinus rhythm 11 years later.

### Case history

A girl found to have a heart murmur in infancy attended the cardiac outpatient clinic at the Royal Hospital for Sick Children, Glasgow, until admitted at the age of 4 years for further investigation. She had no symptoms but the clinical findings were those of a large ventricular septal defect with cardiomegaly (cardiothoracic ratio 60%). The electrocardiogram indicated incomplete right bundle-branch block, left ventricular hypertrophy, and delta waves (Fig. 1). Cardiac catheterization and angiocardiography confirmed the presence of a large ventricular septal defect (Qp:Qs = 2·5:1), with no gradient across the right ventricular outflow, and only mild pulmonary hypertension (35/12 mmHg (4·7/1·6 kPa) in the main pulmonary artery).

Repair was recommended and operation was performed a few weeks later. Through a bilateral anterior thoracotomy and with the support of normothermic cardiopulmonary bypass, the right ventricular outflow was opened to reveal a ventricular septal defect measuring 2 cm in diameter and with a thick muscular inferior margin. A double layer of pericardium was used to close the defect, the main sutures being of mattress type. Over the upper half a continuous suture was used to secure the gap between the main sutures. Third degree atrioventricular block became apparent almost immediately, and pacemaker leads were secured in the right ventricle and pectoralis major muscle. Heart block persisted and the heart was paced continuously during the first 7 postoperative days. Thereafter the pacing wires were removed and oral drug therapy with both prednisolone and ephedrine was instituted. On dismissal from hospital three weeks after operation she was active and free of symptoms in spite of a fixed heart rate of 40 per minute. All drug treatment had been discontinued. Outpatient supervision was maintained, and she remained apparently well but with some limitation in exercise tolerance until five years after operation (1967) when minor Adams-Stokes attacks were recognized. The resting heart rate between attacks was 44 per minute and third degree atrioventricular block persisted (Fig. 2). Long acting isoprenaline ('Saventrine') was introduced, and though the heart rate was not appreciably altered (varying between 40 and 50 per minute) she had no further Adams-Stokes attacks over the next 6 years. Towards the end of 1973 (11 years after operation) she developed episodes of palpitations suggesting paroxysmal supraventricular tachycardia and these were accompanied by chest pain. Because of this she was readmitted to hospital

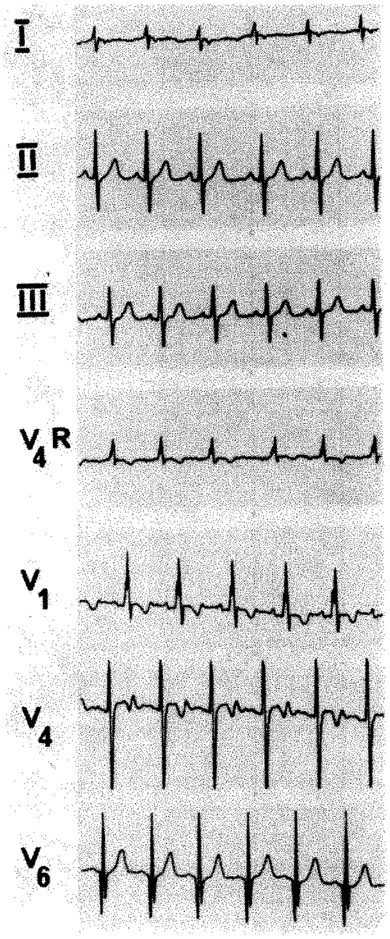

FIG. 1 *Preoperative electrocardiogram, showing sinus rhythm, left axis deviation, and right bundle-branch block. Possible delta waves (type A, pre-excitation) in V1.*

and her resting heart rhythm was found to be sinus tachycardia. After the omission of Saventrine, normal sinus rhythm replaced sinus tachycardia at 120 per minute. A soft, early 2/6 systolic murmur which had been present since operation persisted at the left lower sternal border. There was no cardiac enlargement on the *x*-ray examination. There was right bundle-branch block, and inversion of the T wave in leads V1 to V4 (Fig. 3). Cardiac catheterization confirmed closure of the ventricular septal defect. The echocardiographic appearances were normal. Normal sinus rhythm persists 20 months later.

## Discussion

Third degree atrioventricular block acquired during cardiac surgery is caused by trauma (either haemorrhage or oedema) to the bundle of His as it courses along the caudal edge of the membranous septum. It is regarded as having a poor prognosis (Cooley and Hallman, 1966; Fryda *et al.*, 1971). Fryda *et al.* (1971) reported 40 children with this complication of whom 11 died immediately and 18 reverted to sinus rhythm within the early weeks after operation; of the remaining 11 with persistent block, 6 who were not paced died.

As far as we can discover there have been no previous reports of heart block reverting spontaneously to sinus rhythm after so long an interval as 11 years. Because of the highly unfavourable outlook most authors recommend the implantation of a permanent pacemaker (Cooley and Hallman,

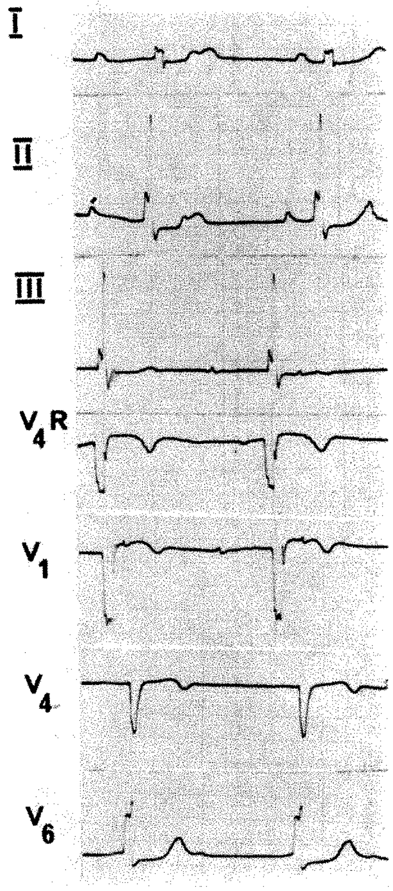

FIG. 2 *Third degree AV block. Electrocardiogram recorded 5 years after operation.*

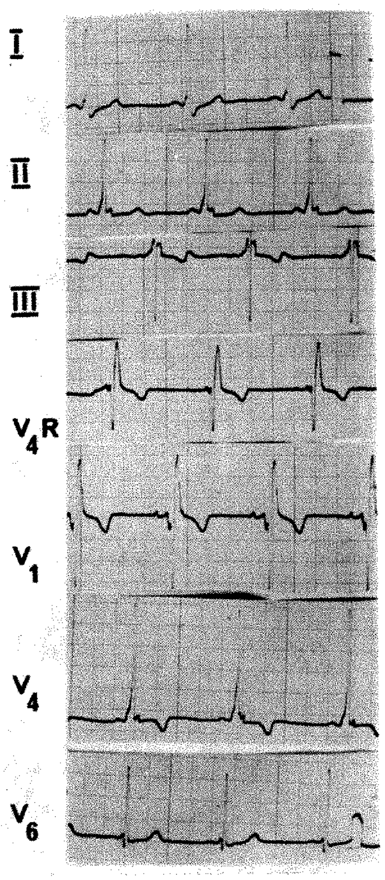

FIG. 3 *Electrocardiogram after spontaneous reversion to sinus rhythm 11 years after operation. Right bundle-branch block is still present.*

1966; Fryda *et al.,* 1971; Nadas and Fyler, 1972). We did not do this because our patient had initially no symptoms attributable to her heart block, and also because the pacemakers available to us at that time (1962) seemed somewhat unreliable. Even when syncopal attacks appeared five years later, these were so easily prevented with long-acting isoprenaline that the implantation of a pacemaker seemed unnecessary. It is difficult to explain the spontaneous return to sinus rhythm after an interval of 11 years. Regeneration of fibres in the bundle of His seems improbable after so long a delay and the development of new accessory pathways is for the same reason difficult to understand.

Perhaps a more tenable but none the less conjectural explanation for the restoration of sinus rhythm would be that the impairment of the conducting system was caused not by direct injury to the pathway but by a surgical manoeuvre causing distortion of the pathway from tension or pressure, and that eventual relief of this functional impairment was related to two features of the 11-year interval, namely, the gradual postoperative restoration of a normal intracardiac architecture and the overall growth of the heart.

The preoperative electrocardiogram suggested the presence of delta waves which are usually found in association with pre-excitation due to an accessory pathway from atrium to ventricle. An alternative and equally attractive explanation, therefore, is that the spontaneous return of sinus rhythm was related to this pathway.

Heart block may arise as a result of damage in either the atrioventricular node or bundle of His, and the site may to some extent influence prognosis. There is evidence to suggest that damage to the bundle of His is not so serious as damage to the node (Wolff, Freed, and Ellison, 1973). To locate the precise site of the block, it is necessary to perform His bundle recordings, and these were not available in our patient.

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# Klippel-Feil syndrome associated with aortic coarctation

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*A 13-year-old boy with aortic coarctation and Klippel-Feil syndrome is reported. This association has not been described previously.*

The triad of low occipital hairline, limitation of neck movement, and fusion of cervical vertebrae was first described by Klippel and Feil (1912) and has come to bear their name. Since then a large number of cases have been described, some with associated congenital anomalies. These include 'Sprengel's' shoulder, rib anomalies, syringomyelia, and cardiac malformations (Menkes, 1974).

## Case report

A 13-year-old boy was admitted for investigation of coarctation of the aorta. At the age of 2 he underwent a laparotomy for bleeding Meckel's diverticulum and the diagnosis of coarctation of the aorta was made at that time. He had no symptoms and school performance was normal. There was no family history of heart disease and his parents and younger brother were well.

On examination he was an intelligent, prepubertal boy, height 147 cm (30th centile) and weight 32 kg (10th centile). A short neck (Fig. 1) and low occipital hairline were noted but facial appearance was normal. There were no abnormalities of the palmar creases. Other relevant physical findings were limited to the cardiovascular system—radial pulses were equal and normal, femoral pulses were absent. The apex beat was not displaced and no thrills were palpable. A grade 2 systolic ejection murmur was audible all over the praecordium and over the scapulae. One collateral vessel was palpable over the right scapula. Blood pressure was 120/70 mmHg (16·0/9·3 kPa) in both arms. Fundi were normal.

Chest *x*-ray film showed early rib notching and there was fusion of the second and third ribs on the right.

Electrocardiogram showed left ventricular hypertrophy by voltage criteria.

In view of his age, aortography was performed under general anaesthesia. At induction, endotracheal intubation proved impossible because of limited extension of the neck and anaesthesia was maintained with a face mask.

Angiography revealed aortic coarctation distal to the left subclavian artery.

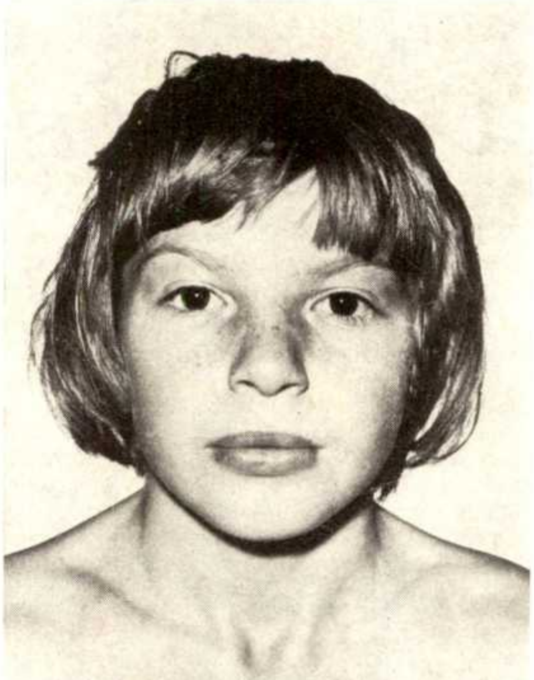

FIG. 1 *The short neck of Klippel-Feil syndrome.*

An *x*-ray film of the cervical spine (Fig. 2) showed fusion of the third and fourth cervical vertebrae and abnormalities of the apophysial joints of C2 and C3. Chromosome analysis of the peripheral blood gave normal results.

Operation was carried out at Walsgrave Hospital by Mr. W. G. Williams. Intubation proved difficult but was eventually achieved in the usual way. There was a severe coarctation rising immediately from the aortic arch, with no proximal segment above the coarctation. The aorta was hypoplastic but not unusual for coarctation. An incision was made in the coarctation extending from the descending aorta to the left subclavian artery and a large 'dacron' patch inserted, with resulting abolition of the gradient across the coarctation. He made an uninterrupted recovery.

## Discussion

A detailed account and review of the published reports on Klippel-Feil syndrome appeared in 1968 (Morrison, Perry, and Scott). These authors collected 19 cases with associated cardiac anomalies out of a total of 503 cases and added 2 cases of their own, giving an incidence of associated cardiac anomalies of 4·2 per cent. Among these 21 cases was a variety of congenital cardiac defects, ventricular septal defect being the commonest (8 cases). No patient had aortic coarctation and none was known to have had a Meckel's diverticulum.

Coarctation of the aorta has a well-known association with chromosomal abnormalities such as Down's syndrome, Turner's syndrome, trisomy 10, and trisomy 13-15. The so-called 'male Turner's syndrome' or Noonan's syndrome is associated with short stature and hypogonadism in males, with a normal sex chromosome complement. There is, however, no increased incidence of aortic coarctation, but pulmonary stenosis may be a feature. Mental retardation is common and webbed neck and cubitus valgus are features. No cervical fusion has been described (Smith, 1970).

In view of the reported increased incidence of congenital heart lesions in Klippel-Feil syndrome and their heterogeneity, it is likely that the association in this patient is genuine rather than fortuitous.

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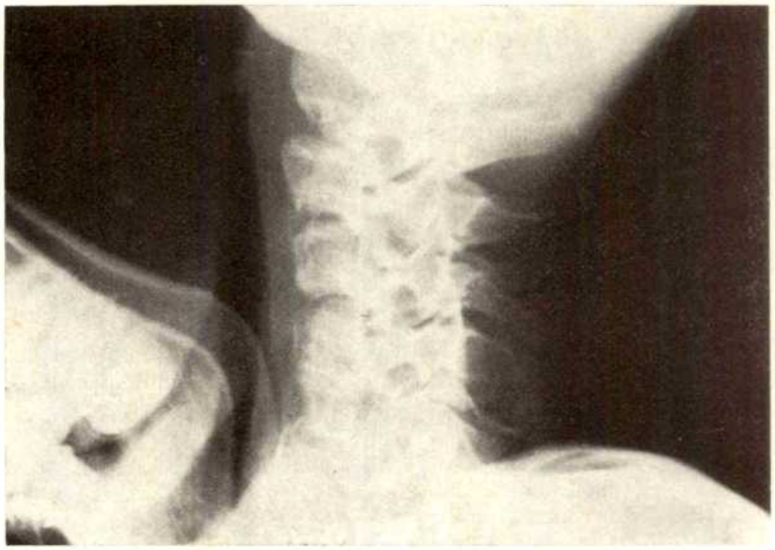

FIG. 2 *X-ray film of the cervical spine showing fusion of the third and fourth vertebrae.*

# *Correspondence*

*British Heart Journal,* 1976, **38,** 1222.

# Left and right heart haemodynamics during spontaneous angina

Sir:

In the past it has been shown that spontaneous angina pectoris associated with electrocardiographic ST segment depression is preceded by a rise in systemic and pulmonary artery pressures in 86 per cent of cases (Roughgarden, 1966).

Recently Guazzi *et al.* (1975, *British Heart Journal,* **37,** 401) showed that no circulatory change was responsible for eliciting spontaneous angina pectoris with ST depression. They found that a fall in arterial pressure and a rise in pulmonary wedge pressure occurred initially, but these were followed by a secondary hypertensive phase during the attack of angina pectoris.

The increased work of the heart caused by a rise in arterial pressure and heart rate is generally considered to be the cause of ischaemia during exercise in patients with clinical angina pectoris.

Roughgarden concluded that the pressure changes of exertional angina resembled those occurring before spontaneous angina. The two authors mentioned seem to have conflicting conclusions for the mechanism of spontaneous angina pectoris.

John M. Bete,
Cape Cod Medical Center,
Hyannis, Massachusetts,
U.S.A.

## Reference

Roughgarden J. W. (1966). Circulatory changes associated with spontaneous angina pectoris. *American Journal of Medicine,* **41,** 947.

This letter was shown to Dr. Guazzi who comments as follows:

The discrepancy which Dr. Bete has noticed between Roughgarden's data and ours is more apparent than real. Dr. Bete probably refers to the summary of Roughgarden's paper when he writes that this author has shown that spontaneous angina pectoris *associated with ST segment depression* is preceded by a rise in systemic and pulmonary artery pressures in 86 per cent of cases, concluding that the pressure changes during exertional angina resemble those before spontaneous angina. Actually, Roughgarden reported that pressure rise in the greater and lesser circulation precedes the onset of anginal pain in 86 per cent of the cases, but the point is that anginal pain and electrocardiographic signs of ischaemia are not synonymous. Myocardial ischaemia and anginal pain (Guazzi *et al.*, 1976), indeed, are two separate phenomena; anginal pain does not necessarily accompany the ischaemia and, when present, never precedes it. In our paper the reference point for the evaluation of the circulatory variations was the onset of the ST segment displacement and not the onset of pain. We have pointed out that no circulatory change, either systemic or pulmonary, precedes the ST segment depression; this led us to conclude that spontaneous myocardial ischaemia is not the result of increased work of the heart.

If Roughgarden's findings are compared with ours with this point in mind, the discrepancy becomes smaller. She found that in only 7 out of 21 monitored episodes of myocardial ischaemia (30% of cases) blood pressure changes preceded the ST segment depression. In these cases, however, the relation of the magnitude and the time of onset of the pressure variations to the electrocardiographic abnormalities was not reported; it is, therefore, difficult to evaluate their significance in producing ischaemia.

Maurizio Guazzi,
Istituto di Ricerche Cardiovascolari
dell' Università di Milano,
Milan, Italy.

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Guazzi, M., Olivari, M. T., Polese, A., Fiorentini, C., and Magrini, F. (1976). Repetitive myocardial ischemia of Prinzmetal type without angina pectoris. *American Journal of Cardiology,* **37,** 923.

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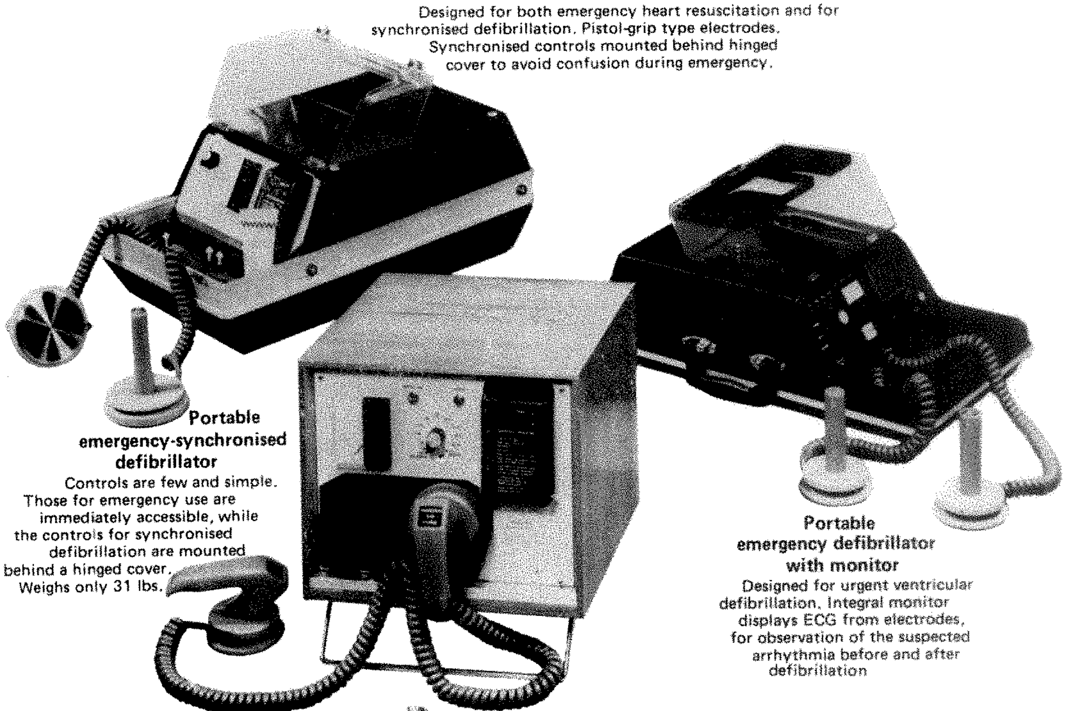

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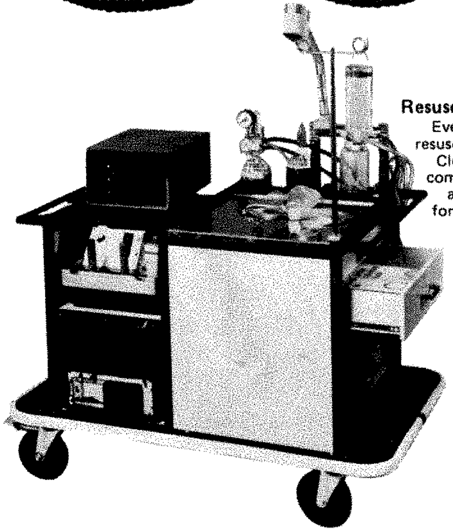

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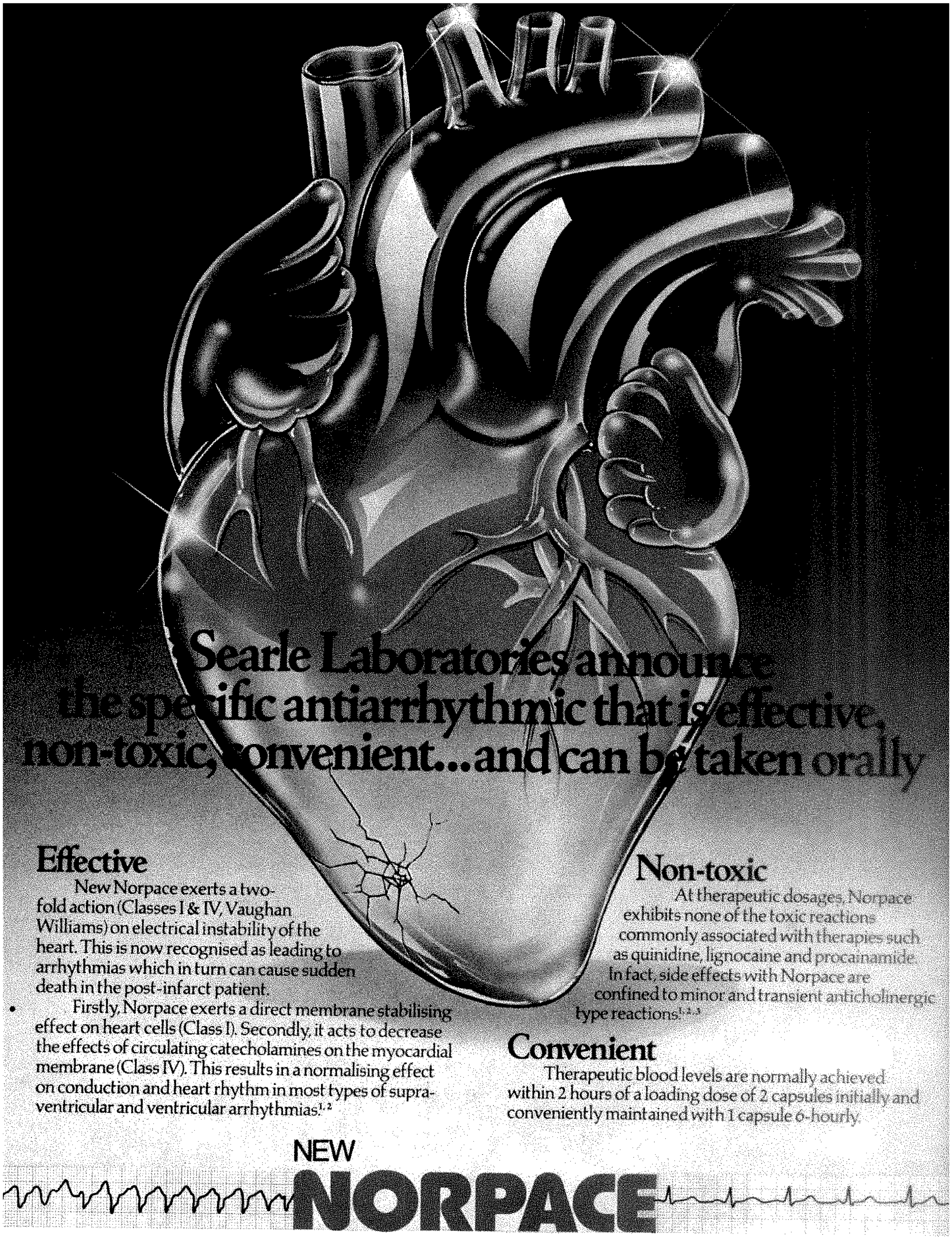

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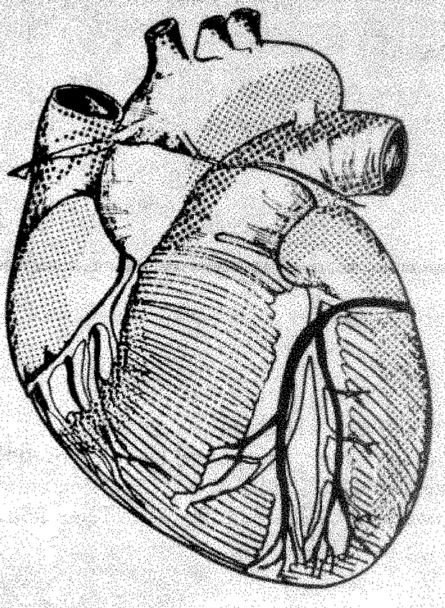

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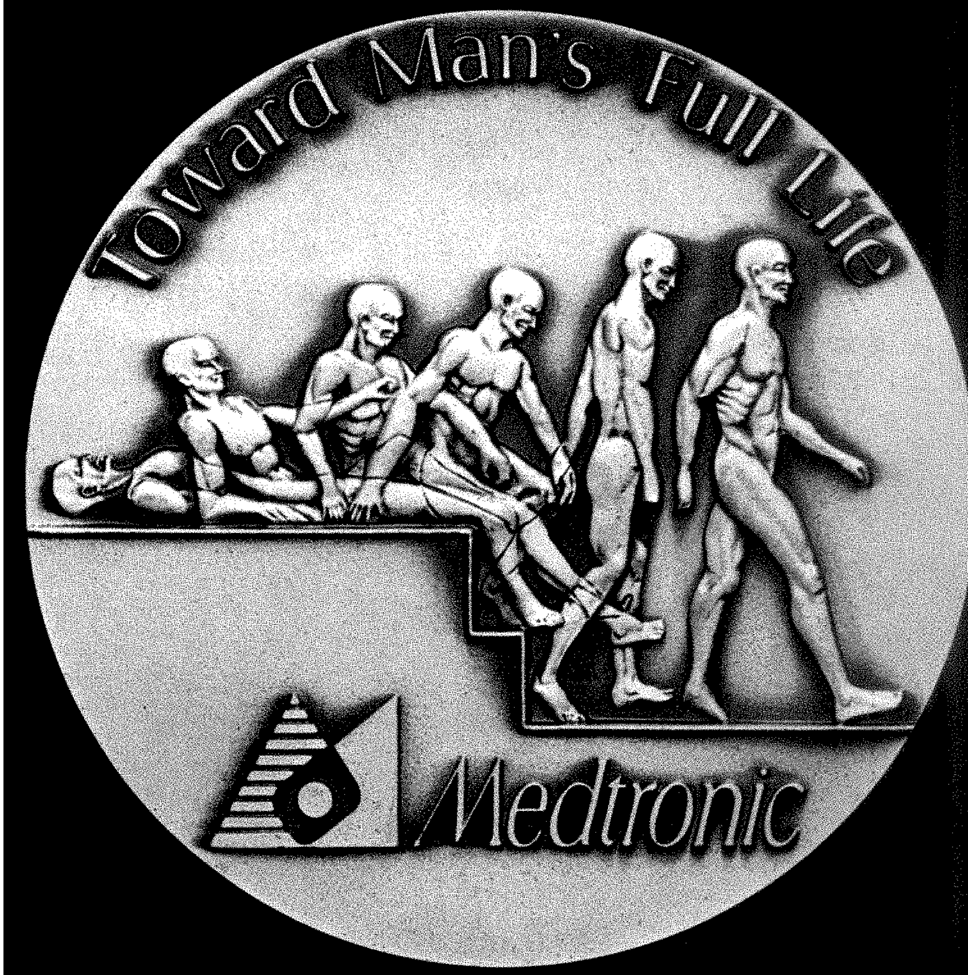

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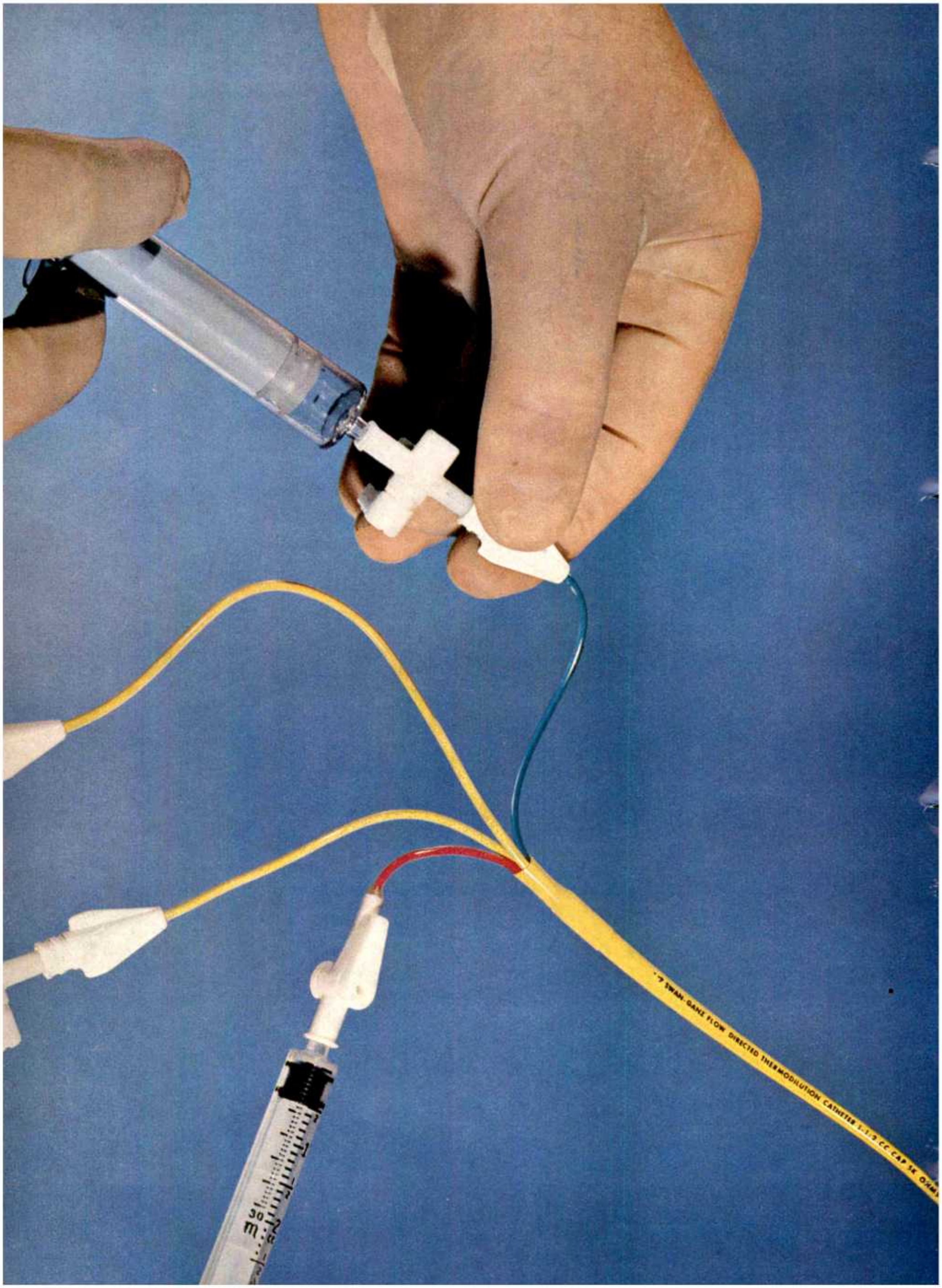
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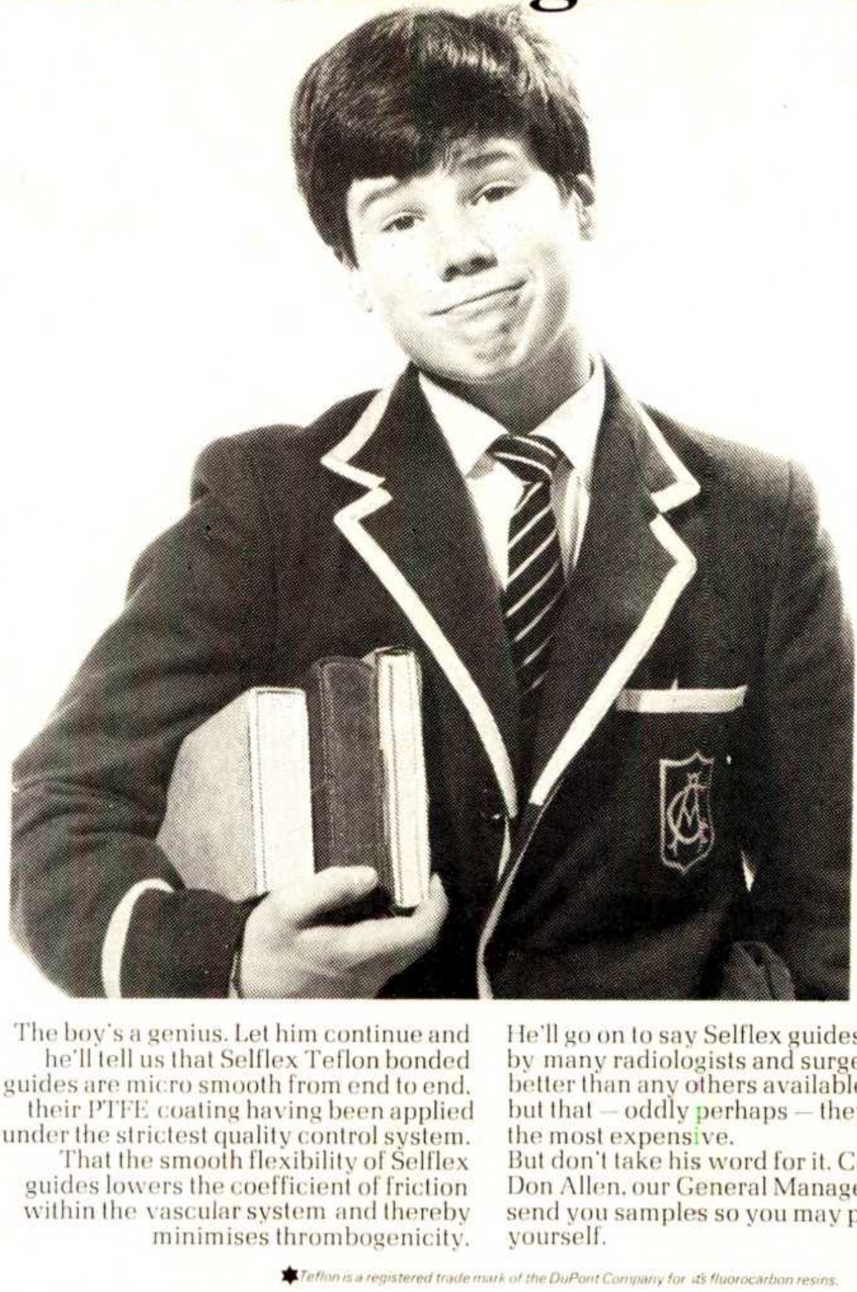

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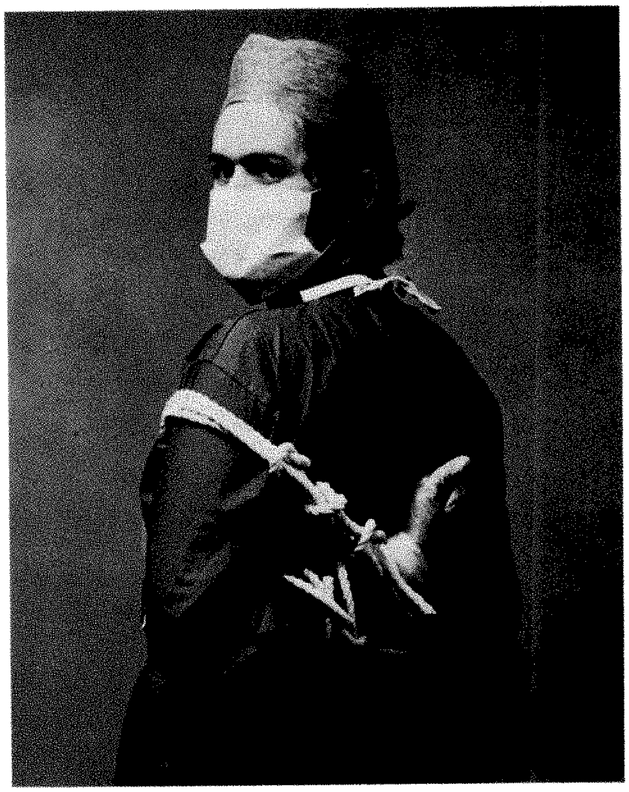

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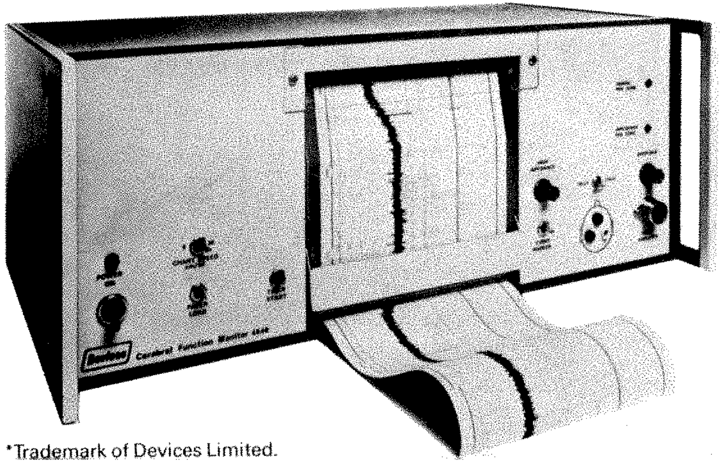

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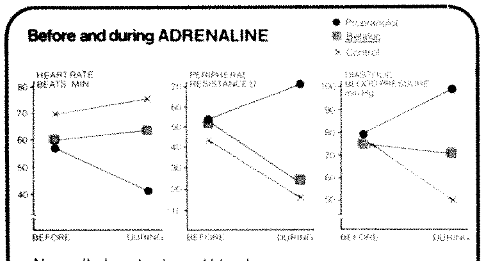
By blocking $\beta_1$ receptors, Betaloc reduces cardiac output and blood pressure. In hypertension, trials have shown that Betaloc is at least as effective as methyldopa or propranolol in controlling blood pressure. In angina, Betaloc has proved superior to propranolol in improving exercise tolerance.

## Avoids unwanted effects

In two commonly occurring situations, non-selective ($\beta_1 + \beta_2$) blockade can produce additional, unwanted effects. Selective $\beta_1$ blockade with Betaloc avoids these potential problems:

### In acute stress[1]

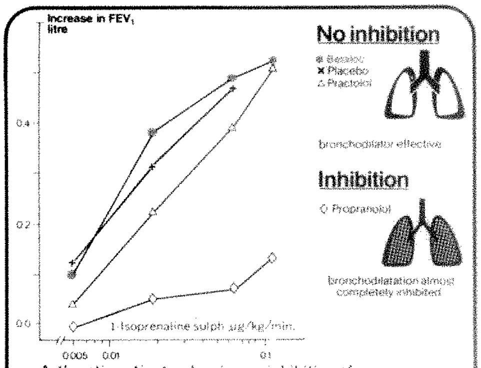
Of particular importance in hypertension – non-selective blockade of peripheral vascular $\beta_2$ receptors may permit dominance of the $\alpha$-receptor (vasoconstrictor) response to adrenaline. The net effect is a drop in cardiac output, with raised peripheral resistance and increased blood pressure. In contrast, selective $\beta_1$ blockade allows the $\beta_2$ receptors to function normally and so maintains control of blood pressure.



Normally, heart rate and blood pressure responses to exercise are inhibited equally by Betaloc and propranolol. During adrenaline infusion (simulating stress) responses differ markedly.

### In asthma or bronchitis[2]

Non-selective blockade of $\beta_2$ receptors may precipitate bronchospasm or inhibit the action of $\beta_2$ stimulating bronchodilators. Because of its $\beta_1$ selective action, Betaloc has no significant effect on lung function and allows the bronchodilator to work.



Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

[1] (1975) *Acta pharmacol et toxi* Suppl. V, 39-68 University of Gothenburg, Sweden.

[2] Clinical Report (1975), University of Gothenburg, Sweden.

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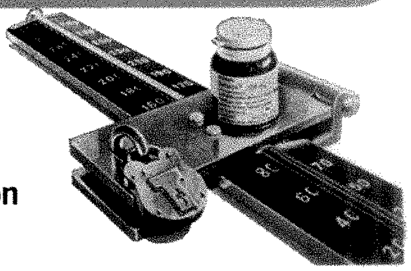

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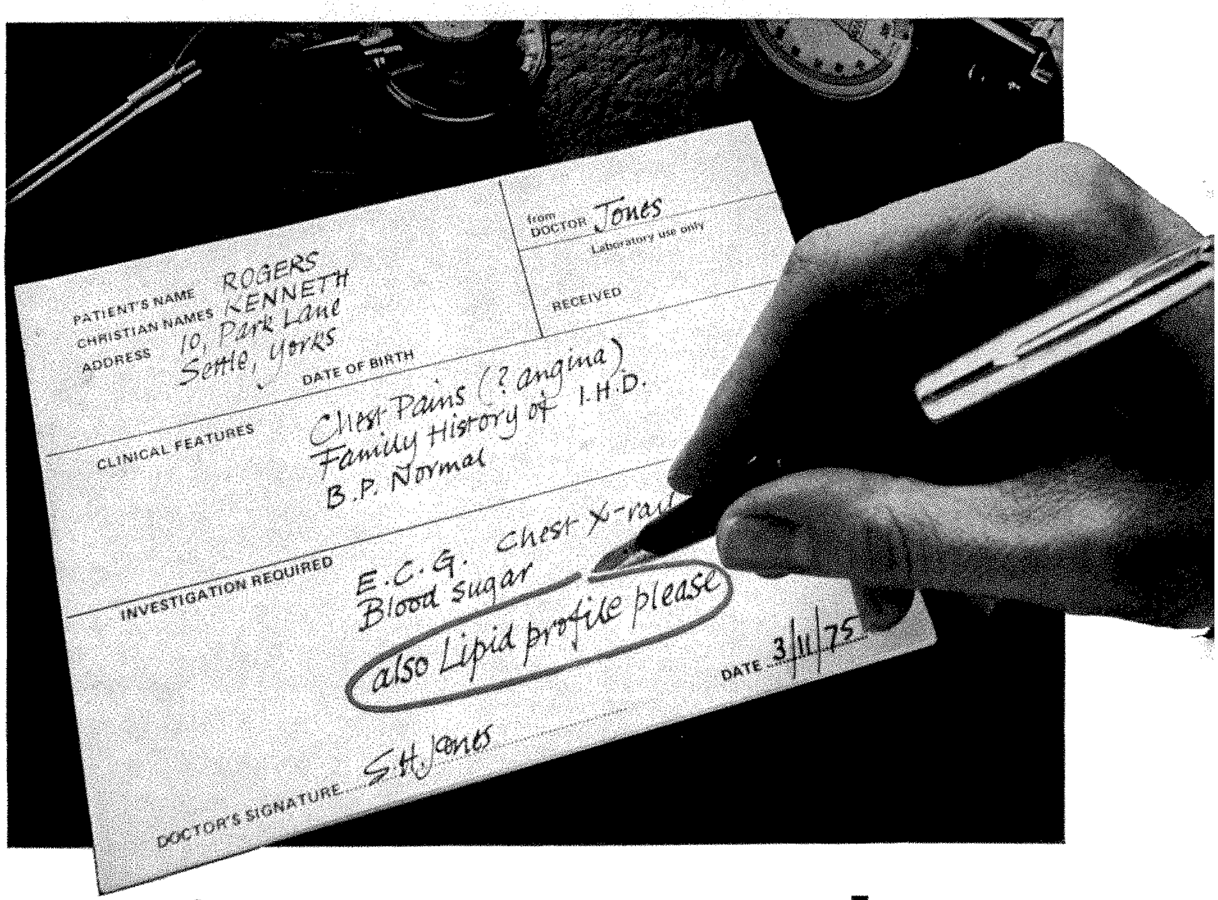

from DOCTOR Jones

Laboratory use only

RECEIVED

PATIENT'S NAME ROGERS
CHRISTIAN NAMES KENNETH
ADDRESS 10, Park Lane
Settle, Yorks
DATE OF BIRTH

CLINICAL FEATURES Chest Pains (? angina)
Family History of I.H.D.
B.P. Normal

INVESTIGATION REQUIRED E.C.G. Chest X-ray
Blood sugar
also Lipid profile please

DATE 3/11/75

DOCTOR'S SIGNATURE S.H. Jones

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REFERENCES
1. Coronary Drug Project Research Group, 1975, *Journal of the American Medical Association* 231, 360.
Product Licence Number 0029/5053.

PH 1337

*British Heart Journal*, 1976, 38, 1223–1228.

# Surgical treatment of postinfarction left ventricular aneurysm in 32 patients

R. M. Donaldson, M. Honey, R. Balcon, S. O. Banim, M. F. Sturridge, and J. E. C. Wright
*From the London Chest Hospital, London*

*Thirty-two patients with large postinfarction left ventricular aneurysms shown at operation to consist of fibrous tissue are reported. All had angina and/or breathlessness, and none had a history of embolism. Thirty were correctly diagnosed by left ventricular cineangiography. Two of the 3 patients with inferior and 1 with an anterior aneurysm had associated ventricular septal defects, and 3 patients with an anterior aneurysm had mitral regurgitation. All had major coronary arterial lesions and 68 per cent had double or triple vessel disease. The aneurysm was excised in all patients; in 15 this was combined with saphenous vein bypass grafting of coronary arteries supplying surviving myocardium, in 3 with closure of a ventricular septal defect, and in 3 with mitral annuloplasty or replacement. Operative mortality was 6·2 per cent, and 79 per cent of the survivors are asymptomatic with average follow-up period of 18 months after operation.*

Postinfarction ventricular aneurysm has been shown to have a poor prognosis (Schlichter, Hellerstein, and Katz, 1954). In addition patients often suffer from exertional dyspnoea associated with a high left ventricular end-diastolic pressure, and from angina due both to increased wall tension in the surviving myocardium (Austen *et al.*, 1962) and to disease of coronary arteries supplying it. For these two reasons, it is appropriate to consider patients for surgical management.

We are reporting here our experience with 32 patients in whom a ventricular aneurysm was excised. In comparing reported series of patients, a major problem is one of definition. Our series includes only those patients who at operation were found to have transmural fibrous scars, clearly delineated from the surrounding muscle, and collapsing when suction was applied to the ventricular vent; the fibrotic nature of the wall of the aneurysm was confirmed by pathological examination of the excised specimen. In many but not all, aneurysm was suspected from the left ventricular angiogram. We have, however, found, like others (Gorlin, Klein, and Sullivan, 1967; Yacoub *et al.*, 1973), that paradoxical outward bulging in systole (dyskinesis) of scarred or poorly perfused but viable myocardium may simulate aneurysm, and that some aneurysms may show akinetic segments but no dyskinesis on the left ventricular angiogram. Some (e.g. Dubnow, Burchell, and Titus, 1965) only classify as aneurysm those scars that are associated with localized protrusion of the external wall of the ventricle as well as of the ventricular cavity. On the other hand, Schlichter, *et al.* (1954) and Mourdjinis *et al.* (1968) include those cases in which there is no external bulge, described by the latter authors as 'minor aneurysms'; our definition which is based on surgical pathological criteria includes such cases.

## Patients

The 32 patients fulfilling these criteria were seen between April 1971 and April 1975. In many of these, ventricular aneurysm was suspected from the clinical features. In most of the others, all of whom were being investigated for coronary heart disease because of symptoms, aneurysm was recognized on the left ventricular angiogram. In 2 the presence of aneurysm was substantiated only at operation.

### Clinical data (Table 1)

There were 27 men and 5 women ranging in age between 27 and 71 years (average 54). Twenty-nine of the patients complained of dyspnoea[1] (average grade 3) and in 25 this was a dominant symptom;

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[1] Angina and dyspnoea were graded 1 to 4 according to New York Heart Association criteria.

TABLE 1 *Clinical details*

| *Case No.* | *Age (y)* | *Sex* | *Dyspnoea* | | *Angina* | | *Limiting symptom* | *Electrocardiogram* | *Chest radiograph* | *Therapy* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Grade* | *Duration (mth)* | *Grade* | *Duration (mth)* | | | | *Beta-adrenergic blocking agent* | *Digoxin/ diuretic* |
| 1 | 71 | F | 2 | 2 | 0 | 0 | D | AMI ST ↑<br>LAHB | Enlarged heart; PVC | 0 | 0 |
| 2 | 45 | M | 3 | 4 | 0 | 0 | D | AMI ST ↑ | Enlarged heart; PVC | 0 | + |
| 3 | 36 | F | 3 | 4 | 0 | 0 | D | AMI ST ↑ | Enlarged heart; PVC | 0 | + |
| 4 | 52 | M | 4 | 1 | 2 | 24 | D | AMI IMI | Enlarged heart; PVC | + | + |
| 5 | 47 | M | 4 | 1 | 0 | 0 | D | AMI ST ↑<br>LAHB | Enlarged heart; pulmonary oedema | 0 | + |
| 6 | 52 | M | 3 | 6 | 1 | 6 | D | AMI ST ↑<br>LAHB | Enlarged heart | + | + |
| 7 | 57 | F | 4 | 6 | 3 | 36 | D | AMI IMI | Enlarged heart; PVC | + | + |
| 8 | 69 | M | 3 | 3 | 0 | 0 | D | AMI ST ↑<br>LAHB | Enlarged heart; PVC | 0 | + |
| 9 | 60 | M | 3 | 24 | 2 | 96 | D | AMI ST ↑ | Enlarged heart; PVC | 0 | + |
| 10 | 63 | F | 2 | 1 | 0 | 0 | D | AMI | Enlarged heart; PVC | 0 | + |
| 11 | 43 | M | 0 | 0 | 0 | 0 | Palpitation | AMI<br>Recurrent SVT | Enlarged heart; calcification | + | 0 |
| 12 | 69 | M | 2 | 5 | 2 | 5 | A/D | IMI | Post-inf. bulge; enlarged heart; pulmonary oedema | 0 | + |
| 13 | 71 | M | 2 | 3 | 2 | 2 | A/D | IMI AMI<br>RBBB | Post-inf. bulge; enlarged heart; PVC | 0 | + |
| 14 | 50 | M | 2 | 6 | 0 | 0 | D | AMI ST ↑<br>LAHB | Normal | 0 | + |
| 15 | 62 | M | 4 | 1 | 0 | 0 | D (cardiogenic shock) | AMI<br>LAHB | Enlarged heart; pulmonary oedema | 0 | + |
| 16 | 67 | M | 4 | 36 | 3 | 36 | A/D | AMI ST ↑ | Enlarged heart; PVC | + | + |
| 17 | 49 | M | 3 | 2 | 1 | 24 | D | AMI ST ↑ | Enlarged heart | + | + |
| 18 | 41 | M | 0 | 0 | 4 | 5 | A | AMI ST ↑ | Normal | + | 0 |
| 19 | 49 | M | 2 | 48 | 3 | 48 | A | AMI ST ↑ | Normal | + | 0 |
| 20 | 63 | F | 4 | 0·5 | 2 | 24 | D (cardiogenic shock) | LAHB<br>AMI<br>(VF ×2) | Enlarged heart; pulmonary oedema | 0 | + |
| 21 | 63 | M | 2 | 3 | 0 | 0 | D | AMI ST ↑ | Enlarged heart; PVC | 0 | + |
| 22 | 27 | M | 1 | 24 | 2 | 24 | A | AMI ST ↑<br>IMI | Enlarged heart | + | 0 |
| 23 | 52 | M | 2 | 4 | 0 | 0 | D | AMI<br>(VF ×2) | Enlarged heart; PVC | 0 | + |
| 24 | 49 | M | 0 | 0 | 3 | 60 | A | AMI | Normal | + | 0 |
| 25 | 62 | M | 2 | 12 | 2 | 180 | A | AMI ST ↑<br>IMI | Enlarged heart; PVC | + | + |
| 26 | 60 | M | 3 | 3 | 0 | 0 | D | AMI<br>LAHB | Enlarged heart; PVC | 0 | + |
| 27 | 62 | M | 3 | 6 | 0 | 0 | D | AMI ST ↑ | Enlarged heart; PVC | 0 | + |
| 28 | 50 | M | 3 | 4 | 3 | 8 | D | AMI ST ↑<br>IMI | Enlarged heart | + | + |
| 29 | 60 | M | 2 | 12 | 2 | 12 | A/D | AMI ST ↑ | Enlarged heart | 0 | + |
| 30 | 67 | M | 3 | 5 | 0 | 0 | D | AMI ST ↑ | Enlarged heart | 0 | + |
| 31 | 44 | M | 2 | 12 | 4 | 12 | A | AMI | Enlarged heart | + | 0 |
| 32 | 55 | M | 3 | 5 | 0 | 0 | D | Junctional rhythm; RBBB | Enlarged heart; post-inf. bulge | 0 | + |

A, angina; D, dyspnoea; AMI, anterior myocardial infarction; IMI, inferior myocardial infarction; ST ↑, persistent ST segment elevation; LAHB, left anterior hemiblock; SVT, supraventricular tachycardia; VF, ventricular fibrillation; PVC, pulmonary venous congestion.

6 patients had dyspnoea at rest, including 2 who were in cardiogenic shock after recent myocardial infarction. Seventeen patients had angina but this was a dominant symptom in only 6. One patient was investigated because of recurrent tachyarrhythmias. All patients had had a previous myocardial infarct between 1 and 16 months before admission, with a typical history and electrocardiogram, and usually enzyme changes; 8 patients had had two such episodes. Two patients had a history of hypertension, one was diabetic, and 19 were smokers. No patient had a history suggestive of arterial embolism. Twenty-five patients were on treatment with digitalis and diuretics for congestive heart failure and 13 with beta-adrenergic blocking agents.

## Investigations

The resting electrocardiogram was abnormal in all, showing evidence of transmural (Q wave) anterior infarction in 24, inferior in 1, and anterior and inferior in a further 6.[1] In 19 patients there was persistent ST segment elevation present for at least 6 months or since infarction if the history was shorter. Left anterior hemiblock (Rosenbaum, Elizari, and Lazzari, 1970) was present in 8. One patient had right bundle-branch block, but no pathological Q waves.

Recurrent supraventricular tachyarrhythmia was recorded in 1 patient, and another had an atrioventricular junctional rhythm. The chest radiograph showed cardiomegaly and/or pulmonary venous congestion in 28 patients, in 4 of whom there was pulmonary oedema. Calcification in the wall of the aneurysm was seen in 1 patient, an abnormality of the left heart border was observed in 22 patients, and a posteroinferior bulge was seen in the lateral radiograph in 3. In 4 patients the cardiac contour was normal. The left ventricular end-diastolic pressure ranged from 6 to 40 mmHg with a mean of 22·3 mmHg (Table 2).

The left ventriculogram showed paradoxical movement in systole in 30 patients, of the anterior wall in 27, and of the inferoposterior wall in 3. In the other 2 cases akinetic segments were seen. Three of the patients with an anterior aneurysm had moderate to severe mitral regurgitation. Ventricular septal defects were present in 2 patients with posteroinferior aneurysms and in 1 patient with an anterior aneurysm. A filling defect compatible with a large thrombus was seen in 10 patients.

Selective coronary angiography was performed in 30 patients, using the Sones technique in all except 1; each major coronary vessel was graded from 0 to 4 on the coronary arteriogram: 0 – normal, 4 – complete occlusion, and 1 to 3 – stenosis of increasing severity. Eight patients had major lesions (grade 3 or 4) of a single vessel, 12 of two vessels, and 10 of three. Two of those with triple vessel disease had additional left main coronary artery stenosis.

## Operation

Three patients had an emergency operation. One of these was admitted in cardiogenic shock 4 weeks after a myocardial infarction; the second deteriorated abruptly after catheterization, and the third was investigated because of a persistent low output state following two episodes of ventricular fibrillation which had been rapidly terminated by cardioversion. The remaining 29 patients had elective procedures.

Operation was carried out using standard normothermic cardiopulmonary bypass. The heart was electrically fibrillated, to prevent embolization which might be caused when handling the heart.

The aneurysms as defined were easily identified thin-walled bulges of the left ventricle. Suction on the left ventricular vent produced collapse of the thin-walled area in all cases. This manoeuvre was useful in delineating the area to be resected. On incising this area the line of demarcation between the viable myocardium and the fibrous aneurysm was easily identified. There were pericardial adhesions overlying the aneurysm in 25 patients. Organized mural thrombus was found in 19 patients. The aneurysm was excised and the left ventricular wound repaired using polypropylene sutures without buttressing with prosthetic material. The major vessel supplying the aneurysmal area was found to have a total or subtotal block in all cases and was not grafted.

Additional operative procedures were undertaken in 18 patients. Fifteen underwent concomitant saphenous vein bypass grafting of vessels not involved in the aneurysm: 7 patients had a single graft, 7 had two grafts, and 1 had three grafts. Aortocoronary bypass was performed by interposition of autologous saphenous vein between the aorta and distal coronary artery, using a single continuous suture for the anastomosis. Two patients with mitral regurgitation, resulting from chordal rupture in 1 and partial papillary muscle rupture in the other, had mitral valve replacement, and a third required annuloplasty. The septum was scarred in most cases, and in 3 patients there were post-infarction ventricular septal defects which were repaired through the open aneurysm. There were 2 surgical deaths (operative mortality 6·2%) resulting from myocardial failure. One of these patients was

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[1] Electrocardiographic criteria for infarction were those of McConahay *et al.* (1970).

TABLE 2 *Results of investigation and operation*

| *Results of investigation* | | | | | | *Operation* | | | *Follow-up* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Case No.* | *Left ventricular end-diastolic pressure (mmHg)* | *Grading of coronary artery lesion* | | | *Other* | *Left ventricular aneurysm* | | *Additional procedure* | *Duration (mth)* | *Symptoms* | *Treatment* |
| | | *Left anterior descending* | *Left circumflex* | *Right* | | *Site* | *Approx. excised area (cm$^2$)* | | | | |
| 1 | 37 | 4 | 0 | 0 | | Ant. | 56 | | 56 | Dyspnoea grade 2 | Digoxin, diuretic |
| 2 | 25 | 4 | 2 | 1 | | Ant. | 56 | | 46 | None | None |
| 3 | 15 | 4 | 0 | 0 | MR 3/4 | Ant. | 70 | Mitral valve replacement | 42 | None | None |
| 4 | 33 | 3 | 4 | 3 | | Ant. | 40 | | Died 16 mth after operation | | |
| 5 | 40 | 4 | 2 | 3 | | Ant. | 150 | | 30 | None | None |
| 6 | 28 | 4 | 3 | 1 | | Ant. | 120 | | 30 | Angina grade 2 | Beta-blocker, digoxin, diuretic |
| 7 | 28 | 4 | 3 | 4 | | Ant.-apical | 45 | VG to RCA | 26 | None | None |
| 8 | 15 | * | * | * | MR 3/4 | Ant. | 40 | Mitral valve replacement | 26 | None | Digoxin, diuretic |
| 9 | 11 | 4 | 3 | 3 | | Ant. | 50 | VG to RCA and CFX; E to RCA | 26 | Angina grade 2 | Beta-blocker |
| 10 | 35 | 4 | 3 | 3 | | Ant. | 150 | | 21 | None | None |
| 11 | 12 | 3 | 2 | 3 | | Ant. | 60 | | 20 | None | None |
| 12 | 20 | 3 | 3 | 4 | VSD | Post-inf. | 15 | Closure VSD; VG to RCA and CFX | 17 | Dyspnoea grade 2 | Diuretic |
| 13 | 35 | 3 | 3 | 4 | VSD | Post-inf. | 6 | Closure VSD; VG to LAD and CFX | 17 | None | Diuretic |
| 14 | 10 | L 4 | 0 | 0 | | Ant. | 40 | | 15 | Postoperative arrhythmias | Beta-blocker |
| 15 | 40 | 4 | 4 | 3 | | Ant. | 120 | | Died at operation | | |
| 16 | 20 | 4 | 2 | 3 | | Ant.-apical | 80 | | Died at operation | | |
| 17 | 15 | 4 | 2 | 0 | | Ant.-apical | 60 | | 14 | None | None |
| 18 | 20 | 4 | 3 | 3 | | Ant. | 15 | VG to LAD and RCA | 14 | None | None |
| 19 | 10 | 3 | 2 | 3 | | Ant. | 28 | VG to LAD | 14 | None | None |
| 20 | 20 | 4 | 2 | 0 | VSD | Ant. | 49 | Closure of VSD | 13 | None | Beta-blocker, diuretic |
| 21 | 6 | * | * | * | | Ant. | 70 | | 10 | None | None |
| 22 | 15 | 4 | 2 | 3 | | Ant. | 32 | VG to RCA and CFX; E to RCA | 10 | None | None |
| 23 | 15 | 4 | 0 | 0 | | Ant.-apical | 45 | | 10 | None | Diuretic |
| 24 | 10 | 4 | 2 | 4 | | Apical | 21 | VG to LAD and RCA; E to RCA | 7 | None | None |
| 25 | 12 | L 4 | 3 | 4 | | Apical | 54 | VG to RCA; CFX, and LAD | 7 | None | Digoxin, diuretic |
| 26 | 25 | 3 | 3 | 0 | MR 2/4 | Ant.-apical | 36 | VG to CFX; mitral annuloplasty | 7 | Dyspnoea grade 1 | Diuretic |
| 27 | 35 | 4 | 0 | 2 | | Ant. | 80 | | 7 | None | None |
| 28 | 17 | 3 | 2 | 4 | | Ant.-apical | 50 | VG and E to RCA | 6 | None | None |
| 29 | 22 | 4 | 3 | 1 | | Ant. | 24 | VG to CFX | 6 | None | None |
| 30 | 25 | 4 | 2 | 3 | | Ant.-apical | 40 | VG to RCA | 6 | None | None |
| 31 | 35 | 4 | 3 | 4 | | Ant. | 80 | VG to RCA and CFX | 6 | None | None |
| 32 | 25 | 0 | 4 | 4 | | Post-inf. | 150 | VG to RCA | 6 | None | None |

*No coronary arteriogram.

MR, mitral regurgitation (grade); VSD, ventricular septal defect; L, left main coronary artery stenosis; VG, vein graft; E, endarterectomy; LAD, left anterior descending coronary artery; CFX, left circumflex coronary artery; RCA, right coronary artery.

in cardiogenic shock after a massive recent infarction, the other patient had dyspnoea at rest. There were no deaths in the early postoperative period.

All patients were treated with anticoagulants for three months; digoxin and diuretics were used initially and discontinued when possible (Table 2).

## Pathology

The resected portion of the left ventricle was examined histologically in 30 patients, and was composed of hyalinized fibrous tissue, with a few residual muscle bundles in most cases. The size of the aneurysm ranged from 3×2 to 15×10 cm (average 62 cm$^2$); one was heavily calcified over 6 cm$^2$.

## Follow-up

This ranged from 6 to 56 months (average 17·8 months). One patient with severe triple vessel disease who did not undergo coronary revascularization had a further myocardial infarction 6 months after operation and died of congestive cardiac failure less than a year later. Cardiovascular symptoms and exercise tolerance improved considerably in all patients. Of the 29 survivors, 18 are now leading a normal active life without drug therapy, 5 are asymptomatic on standard anti-failure treatment, requiring less diuretic than in the preoperative period; 2 patients have grade 2 dyspnoea and 1 patient has grade 1 dyspnoea in spite of medical treatment. One patient has recurrent postoperative atrial tachyarrhythmias, partially controlled with beta-adrenergic blocking drugs. Two patients still have grade 2 angina pectoris. One of these did not have vein graft surgery in spite of major lesion in the circumflex artery. The other has been reinvestigated: left ventriculography showed conspicuous improvement in left ventricular function with effective resection of the aneurysmal area; the right coronary artery graft was occluded.

## Discussion

Angiographic criteria for the diagnosis of left ventricular aneurysm are not generally agreed and are unreliable. Since many reported series depend upon the angiogram for diagnosis it is difficult to compare their surgical results. Our patients all had fibrous aneurysms seen at operation and confirmed in the majority by pathological examination of the specimen. The only other series where the same criteria were used was from the Cleveland Clinic (Loop *et al.*, 1973a). The diagnosis had been made before operation in all except 2 of our patients by the observation of paradoxical movement of a segment of myocardium in systole seen on the left ventriculogram (Gorlin *et al.*, 1967). In our experience, however, the left ventriculogram is not diagnostic in the sense that sometimes we have suspected aneurysm because of paradoxical wall movement, but at subsequent operation a fibromuscular hypokinetic area was found. This difficulty has been noted by others (Yacoub *et al.*, 1973).

All of our patients presented with cardiac symptoms and were investigated for this reason. It is interesting to note, however, that there was no history of systemic emboli despite the fact that 59 per cent of the patients had mural thrombus at the time of operation. A similar incidence of mural thrombus has been previously reported by Dubnow *et al.* (1965) (65%) and by Schlichter *et al.* (1954) (54%), though these authors also reported a high incidence of arterial emboli (38% and 64%, respectively); however, both these studies were based on post-mortem material. The Cleveland Clinic group (Loop *et al.*, 1973a) also found that arterial emboli were uncommon; the symptomatology of our patients was in fact similar in most respects to theirs. Other reported series are heavily weighted by patients with one or other dominant symptom, e.g. angina (Rao *et al.*, 1974), congestive cardiac failure (Cooperman *et al.*, 1975), ventricular tachycardia (Hazan *et al.*, 1973). The majority of our patients had persistent dyspnoea after treatment with digitalis and diuretics, and some had frank pulmonary oedema, but more than half also had angina pectoris and this was the dominant symptom in 6 patients. This high incidence of angina was associated with severe coronary disease; only 8 of our patients had an isolated lesion of the left anterior descending coronary artery which was the finding in the majority of patients in the earlier reports (Cooley *et al.*, 1958; Favoloro *et al.*, 1968; Cooley and Hallman, 1968). The differences in patient selection may explain the widely varying operative mortality that has been reported, ranging from nil (Rao *et al.*, 1974) to 32 per cent (Kay *et al.*, 1970). The series reported by Rao *et al.* (1974) differed from others in that angina was the presenting symptom in 75 per cent of the patients. Our operative mortality figure of 6·2 per cent is very similar to that of Loop *et al.* (1973a) whose group of patients most closely resembled ours.

Additional aortocoronary bypass grafting was not routine at the beginning of the series but became so later when 15 patients had this done. This has been the common course of events (Merin *et al.*, 1973;

Loop *et al.*, 1973a; Cooperman *et al.*, 1975). Most of the aneurysms excised were large and only in 3 was the area excised less than 20 cm$^2$. It is not possible to compare this with other surgical series as the area of aneurysm is usually not stated.

The patients who in addition had a ventricular septal defect closed or mitral annuloplasty or valve replacement all survived. A feature of interest in this series is the presence of 2 patients with a large posteroinferior aneurysm in association with a ventricular septal defect. The rarity of posteroinferior aneurysms has been previously observed (Loop *et al.*, 1973b) and in a very large series of 400 patients there were only 11 such cases, in 2 of whom there was an associated ventricular septal defect; both of these patients also survived operation, and showed great symptomatic improvement.

The majority of our patients have improved clinically and 18 are asymptomatic leading a normal life without medical therapy. Only one patient is worse, with increased severity of angina. There has only been 1 late death, 16 months after operation.

Loop *et al.* (1973a) have attempted to compare surgical with medical treatment and have suggested that the expectation of life is substantially improved by aneurysmectomy. The medical prognosis is, however, judged from post-mortem data which may well be unrepresentative (Schlichter *et al.*, 1954; Dubnow *et al.*, 1965). Data available on the expected mortality of patients with coronary disease and left ventricular dysfunction also suggest a high mortality in patients treated medically; for example, Bruschke, Proudfit, and Sones (1973) report a 46 per cent 5-year cardiac mortality in patients showing dyskinesis (aneurysm) in the left ventricular angiogram.

The low operative mortality, the excellent results in terms of symptomatic relief, and the improved expectation of life after excision of left ventricular aneurysms suggest that operation should be advised in these patients. Aneurysmectomy can be safely combined with aortocoronary bypass grafting, closure of ventricular septal defect, or correction of mitral regurgitation when these additional procedures are indicated.

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# Left ventricular function in chronic renal failure

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*Left ventricular function was studied in 14 patients with end-stage chronic renal failure using non-invasive methods (echocardiography and systolic time intervals). Patients were divided into 3 groups. Group 1 consisted of 5 patients who were normotensive at the time of study and group 2 of 7 patients who were hypertensive when studied. Group 3 consisted of 2 patients: one was receiving propranolol and the other, studied 302 days after renal transplantation, was receiving digitalis for recurrent episodes of cardiac failure.*

*All except the patient receiving propranolol had normal left ventricular function in systole with normal measurements of fractional fibre shortening (% $\Delta S$, EF) and normal measurements relating to the velocity of ventricular contraction (mean Vcf, mean velocity of posterior wall motion). Stroke volume and cardiac output were normal in some patients but were increased in patients with fluid overload. Early diastolic compliance of the left ventricle seemed to be normal except in the patient with recurrent cardiac failure. The study provided no evidence for the existence of a specific uraemic cardiomyopathy.*

Cardiac failure is common in patients with chronic renal failure, but its mechanism is uncertain. The existence of a specific uraemic cardiomyopathy has been suggested, but there are no detailed studies of left ventricular function in patients with chronic renal disease (Agrest and Finkielman, 1967; Del Greco *et al.*, 1969; Gueron *et al.*, 1975; Prosser and Parsons, 1975).

Non-invasive techniques are now widely used in the assessment of cardiac performance (Weissler, 1974). The data obtained correlate well with measurements made at cardiac catheterization, and the non-invasive methods have the advantage that they can be made and repeated at the bedside without distressing or harming the patient. Non-invasive techniques include the recording and measurement of the time intervals of the cardiac cycle (Weissler, Peeler, and Roehll, 1961; Weissler, Harris, and Schoenfeld, 1968; Kumar and Spodick, 1970; Lewis *et al.*, 1973) and echocardiography (Feigenbaum, 1972; Fortuin, Hood, and Craige, 1972; McDonald, 1974). We have used the systolic time intervals and echocardiography to study myocardial performance in detail in a group of patients with chronic renal failure.

## Patients

Fourteen patients with chronic renal failure were studied. The clinical data are given in Table 1. The patients were divided into 3 groups: 5 patients were normotensive at the time of study (group 1) (BP $<$140/90 mmHg). Two of these had been hypertensive and the blood pressure reduced effectively with treatment. Seven patients were hypertensive (group 2) (BP $>$150/100 mmHg). Two patients were classified separately (group 3): 1 patient (Case 13) was studied 302 days after renal transplantation; he had had recurrent episodes of cardiac failure and was receiving digitalis. The other patient (Case 14) had been hypertensive, but was being treated with a beta-adrenergic blocking drug (propranolol) at the time of study. Several patients were receiving other drugs: these are shown in Table 1.

One patient in group 1 (Case 3) and 3 patients in group 2 (Cases 10, 11, and 12) were very ill at the time of study because of severe fluid overload and were dialysed peritoneally immediately after the cardiac measurements were made. The data from these patients were compared with those of patients not in frank cardiac failure.

All patients were anaemic and had raised serum urea and creatinine levels: there was no difference in these measurements between groups 1 and 2 (unpaired t-test). One patient in group 1 (Case 3) was an elderly man who had chronic obstructive airways disease and one in group 2 (Case 9) had overt coronary artery disease with an ischaemic resting electrocardiogram. The patient studied after renal transplantation had an arteriovenous

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TABLE 1 *Clinical and biochemical data*

| *Case No.* | *Age* | *Sex* | *Diagnosis* | *Pulse (beats/min)* | *Arterial BP (mmHg) S/D* | *(mean)* | *JVP (cm)* | *Oedema* | *Apex beat* | $S_3$ | $S_4$ | *Hb (g/dl)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group 1: normotensive patients* | | | | | | | | | | | | |
| 1 | 57 | F | AN | 80 | 130/80 | (97) | 0 | 0 | LV++ | – | + | 8·0 |
| 2 | 46 | F | AN | 86 | 140/80 | (100) | 0 | 0 | LV+ | – | + | 8·6 |
| 3 | 66 | M | Amyloidosis+COPD | 90 | 130/90 | (103) | +2 | + | Not palpable | – | – | 5·8 |
| 4 | 54 | F | Chronic renal failure | 70 | 140/80 | (100) | 0 | 0 | Normal | – | – | 9·9 |
| 5 | 29 | F | CPN | 80 | 140/80 | (100) | 0 | 0 | Normal | – | – | 7·5 |
| Mean ±SD | 50 ±14 | | | 81 ±8 | | (100 ±2) | | | | | | 8·0 ±1·5 |
| *Group 2: hypertensive patients* | | | | | | | | | | | | |
| 6 | 29 | M | CGN | 70 | 190/112 | (138) | 0 | 0 | LV+ | – | – | 10·5 |
| 7 | 40 | M | AN | 75 | 160/106 | (124) | 0 | 0 | LV+ | – | + | 10 0 |
| 8 | 43 | F | SLE | 75 | 170/100 | (123) | 0 | + | LV+ | – | + | 7·4 |
| 9 | 57 | M | CGN+CAD | 100 | 150/100 | (117) | +5 | 0 | LV+ | + | – | 6·9 |
| 10 | 29 | M | MGN | 75 | 180/130 | (147) | +3 | 0 | LV++ | – | + | 5·2 |
| 11 | 43 | M | CGN | 100 | 190/120 | (143) | +5 | 0 | LV++ | – | + | 10·3 |
| 12 | 48 | M | AN | 100 | 200/110 | (140) | +4 | 0 | LV++ | – | + | 7 9 |
| Mean ±SD | 41 ±10 | | | 85 ±14 | | (133 ±12) | | | | | | 8·3 ±2·0 |
| *Group 3: miscellaneous* | | | | | | | | | | | | |
| 13 | 44 | M | Post-transplantation | 60 | 160/80 | (106) | 0 | 0 | LV++ | + | – | 7·1 |
| 14 | 35 | F | CGN: On propranolol | 80 | 160/90 | (113) | 0 | 0 | LV++ | + | + | 5·7 |

AN, analgesic nephropathy; CAD, coronary artery disease; CGN, chronic glomerulonephritis; COPD, chronic obstructive airways disease; CPN, chronic pyelonephritis; MGN, membranous glomerulonephritis; SLE, systemic lupus erythematosus.
*Conversion from SI Units to Traditional Units: Urea:* 1 mmol/l≈6·024 mg/100ml; *creatinine:* 1 mmol/l≈0 0113 mg/100 ml.

shunt at the time of study. Fistulae or shunts were not present in the other patients.

## Methods

Patients were studied in a comfortable semi-recumbent position. The systolic and diastolic time intervals of the cardiac cycle were measured from simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and carotid pulse tracing or apex cardiogram (ACG), using a Cambridge multi-channel photographic recorder and a paper speed of 100 mm/s. The apex cardiogram was recorded with the patient in the left lateral position since this provides high quality recordings for measurement. An air-filled funnel transducer was used for the carotid and apex recordings.

Measurement of the systolic time intervals was followed immediately in 9 patients by echocardiography, using an Ekoline 20 machine (Smith-Kline Instruments). A C-12 2·25 MHz focused transducer was used. The transducer was placed in the 3rd to 5th interspace near the left sternal border and carefully directed to obtain, successively, echocardiographic recordings of the mitral valve, aortic root-left atrium, and the left ventricle according to standard techniques (Feigenbaum, 1972; Popp *et al.*, 1975). A permanent record of the echocardiograms was made with a polaroid camera.

Serial studies of left ventricular function were made on Case 12. Measurements were made immediately before dialysis and repeated 3 hours after a 40-hour peritoneal dialysis during which the patient lost 4 kg in weight.

## Data analysis

### (1) Time interval measurements

**(a) Systolic measurements** (Fig. 1) *Pre-ejection period (PEP)* is the time from the first deflection of the QRS complex on the electrocardiogram to the onset of the rapid upstroke of the carotid pulse tracing, which corresponds to aortic valve opening. PEP must be corrected for pulse transmission time delay; this was done by comparing the timing of the dicrotic notch of the carotid

| *Urea (mmol/l)* | *Creatinine (mmol/l)* | *K+ (mmol/l)* | *Drugs* |
|---|---|---|---|
| 18 | 902 | 4·6 | Methyldopa, frusemide |
| 20 | 557 | 5·2 | Methyldopa, frusemide |
| 35 | 1353 | 6·3 | Nil |
| 36 | 1185 | 4·1 | Chlorthalidone |
| 41 | 1291 | 5·1 | Nil |
| 30 ± 10 | 1061 ± 327 | 5·1 ± 0·8 | |
| 22 | 831 | 5·0 | Methyldopa, chlorothiazide |
| 25 | 690 | 4·4 | Methyldopa |
| 29 | 318 | 3·5 | Methyldopa, bethanidine, frusemide |
| 32 | 1105 | 5·7 | Frusemide |
| 40 | 1777 | 5·4 | Nil |
| 37 | 1025 | 4·5 | Methyldopa; hydrallazine, frusemide |
| 49 | 2122 | 5·0 | Nil |
| 34 ± 9 | 1123 ± 628 | 4·8 ± 0·7 | |
| 19 | 292 | 3·5 | Digoxin, frusemide, clonidine, azathioprine, prednisolone |
| 35 | 1512 | 5·8 | Propranolol (20 mg tds) |

pulse tracing with the aortic component of the second heart sound (A2). PEP has 3 components: the electromechanical interval (which cannot be measured), the time from mechanical activation to the time of left ventricular pressure rise, and the *isovolumic contraction time (ICT)*. ICT may be calculated from apex cardiogram ($ICT_{ACG}$) or from phonocardiogram ($ICT_{PCG}$), thus:

$$ICT_{ACG} = PEP-(Q\text{-}U_{ACG})$$

where $Q\text{-}U_{ACG}$ = time from QRS onset to the upstroke of apex cardiogram (ACG)

and $$ICT_{PCG} = PEP-(Q\text{-}M1)$$

where Q-M1 is the time interval from QRS onset to the first high frequency component of the first heart sound.

We used $ICT_{ACG}$ since it is more accurate: $U_{ACG}$ corresponds to the onset of LV pressure rise and does not depend on changes in loading conditions (Kumar and Spodick, 1970). PEP and ICT are useful measurements of cardiac function and are closely related to the isovolumic velocity indices of LV function (peak LV dp/dt; $V_{max}$) but are also affected by LV end-diastolic pressure and aortic diastolic pressure.

*Left ventricular ejection time (LVET)* is the time from aortic valve opening to aortic valve closure and is measured from the upstroke of the carotid pulse tracing to the nadir of its dicrotic notch. LVET is related to stroke volume, afterload, and heart rate; it also depends ultimately on the state of myocardial contractility.

*Total electromechanical systole* ($Q\text{-}A_2$) is the sum of PEP and LVET.

The STI measurements (except ICT) are rate-dependent. We calculated ΔPEP, ΔQ-M1, ΔLVET, and ΔQ-A2 where the Δ value is the dif-

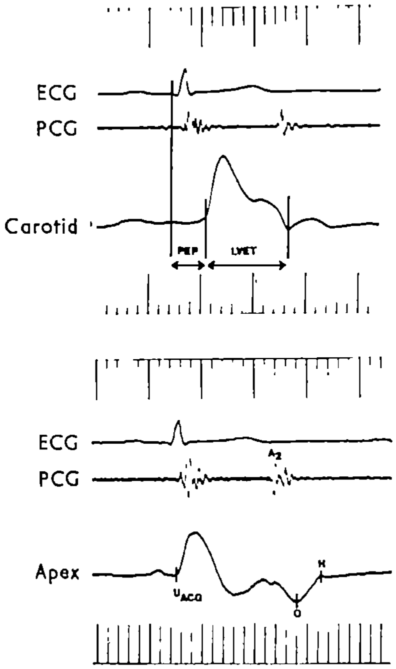

FIG. 1 *Method for measuring the time intervals of the cardiac cycle.* Upper panel: *simultaneous recording of the electrocardiogram (ECG), phonocardiogram (PCG), and external carotid pulse tracing. Pre-ejection period (PEP) is the time from the onset of the QRS complex to the upstroke of the carotid pulse, after correction for pulse transmission time delay. Left ventricular ejection time (LVET) is measured from the carotid upstroke to its dicrotic notch.* Lower panel: *simultaneous recording of ECG, PCG, and apex cardiogram permits calculation of the isovolumic contraction time (PEP minus $Q\text{-}U_{ACG}$), isovolumic relaxation period (A2-O), and rapid filling phase (O-H).*

ference between the measured value and the normal predicted value for a given heart rate (Weissler *et al.*, 1968).

The *ratio PEP/LVET* was calculated. This ratio magnifies abnormalities of cardiac function and is related to ejection fraction (Garrard, Weissler, and Dodge, 1970).

**(b) Diastolic measurements** *Isovolumic relaxation period (IRP)* was measured as the time interval from A2 on the PCG to the 0 point of the apex cardiogram[1]. The *O-H time* is the duration of the rapid ventricular filling phase and was measured on the apex cardiogram (Fig. 1).

All systolic time interval measurements were made by a single experienced observer and the mean values over several cardiac cycles were used. Measurements were corrected to the nearest 5 ms. The apex cardiogram was difficult to record in patients with a large chest wall or in those who were distressed: for this reason ICT, IRP, and the O-H time were not calculated in all patients.

### (2) Echocardiographic measurements

**(a) Length and volume measurements** The diameter of the left ventricle in its minor axis was measured at end-diastole (Dd) and at end-systole (Ds). Percentage dimension change (% Δs) was calculated:

$$\% \Delta S = \frac{Dd - Ds}{Dd} \times 100\%$$

Left ventricular volumes were derived from the cube of the single-plane diameter measurements (Feigenbaum, 1972; McDonald, 1974). End-diastolic (EDV) and end-systolic volume (ESV) were calculated and stroke volume (SV) and ejection fraction (EF) were derived. Ejection fraction (EF) is the volume equivalent of the linear measurement (% ΔS).

$$EF = \frac{EDV - ESV}{EDV} \times 100\%$$

Cardiac output (CO) was obtained from the formula

CO (l/min) = SV (ml) × heart rate (beats/min).

**(b) Velocity measurements of left ventricular function** Velocity measurements were derived from a combination of echocardiographic and time interval data. The mean velocity of circumferential fibre shortening (mean Vcf) is considered a good ejection phase index of ventricular performance (Karliner *et al.*, 1971; Skloven *et al.*, 1972; Ross, Covell, and Mahler, 1974; Quinones *et al.*, 1975).

$$\text{Mean Vcf} = \frac{Dd - Ds}{Dd \times LVET} \text{ (circ/s)}$$

We also measured the velocity of posterior LV wall motion (Vpwm), using the formula:

$$\text{Mean Vpwm} = \frac{\text{Total pwm during ejection}}{LVET} \text{ (mm/s)}$$

**(c) Diastolic function of the left ventricle** The diastolic closure rate of the anterior mitral leaflet (mitral DCR; EF slope) was measured from 3 to 5 complexes showing maximal amplitude of anterior mitral leaflet excursion; the EF slope was essentially monophasic in all the echocardiograms. In the absence of mitral valve disease the EF slope is related to stroke volume and left ventricular pressure-volume relations (Quinones *et al.*, 1974).

### Critique of methods

**Echocardiographic data** These are now widely used in studies of left ventricular function but must be analysed critically (Linhart *et al.*, 1975). The single-plane echocardiogram measures a single diameter of the left ventricle. Calculations of ventricular volume assume a constant relation between this diameter and the volume of the left ventricle: this assumption may not be valid in patients with hypertrophied, volume-overloaded, or irregularly shaped ventricles. Absolute measurements of left ventricular volumes and cardiac output may, therefore, be inaccurate, but this criticism does not apply to the diameter measurements themselves, to the velocity measurement Vcf, and to measurements of fractional fibre shortening (% ΔS; EF). We used polaroid echocardiographic recordings: small errors in measurement are magnified when the diameter and volume measurements are computed. For these reasons echocardiographic measurements of left ventricular function were made in only 8 patients, from whom high quality recordings were obtained.

*Statistical analysis* of differences in the results between groups was not performed since the number of patients in each group was small. Normal values for STI and echocardiographic measurements are taken from large series of published reports (Weissler *et al.,* 1968; Kumar and Spodick, 1970; McDonald *et al.,* 1972).

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[1] The time interval A2-0 point is an approximation of the isovolumic relaxation period, since the mitral valve opens and significant ventricular filling occurs before the 0 point (Prewitt *et al.*, 1975). This time interval is better called 'ventricular relaxation period' though we have retained the term 'isovolumic' for uniformity with other published studies. The 0 point of the apex cardiogram corresponds very closely to the 0 point of the left ventricular pressure pulse, the nadir of the ventricular pressure pulse tracing in early diastole (Manolas *et al.*, 1975).

## Results

The results are summarized in Tables 2 to 4.

### **Time interval measurements** (Table 2)

PEP and ΔPEP were normal in most patients in group 1 and increased in some patients in group 2 ($p > 0·05$). The increase in ΔPEP seemed to be related to a high arterial diastolic pressure (Fig. 2). An increase in ΔPEP, however, was also related to an increase in ΔQ-M1 ($r = 0·77$, $P < 0·01$) (Fig. 3), indicating that in some patients ΔPEP may have been increased by a greater preload. ICTACG was normal or decreased and this finding suggests an increased velocity of ventricular contraction. This implies that myocardial contractility was good in spite of abnormal loading conditions sufficient to affect ΔPEP and ΔQ-M1.

LVET and ΔLVET were normal in most patients. ΔLVET was slightly longer in 2 patients in group 2 (hypertensive patients). LVET and ΔLVET were decreased in Case 14, who was taking propranolol, and in Case 4, in whom all systolic time interval measurements were decreased and for which no apparent explanation was present.

The ratio PEP/LVET reflected the changes in PEP and LVET and was increased in patients in group 2 who had a prolonged PEP. It was also increased in the older patient with chest disease (Case 3 in group 1). PEP/LVET was not related to ejection fraction, as calculated from the echocardiogram. Total electromechanical systole ($Q\text{-}A_2$) was normal in most patients, though perhaps slightly

TABLE 2 *Time interval measurements*

| *Case No.* | *HR (beats /min)* | *PEP (ms)* | *ΔPEP (ms)* | *LVET (ms)* | *ΔLVET (ms)* | *PEP/ LVET* | *ICT$_{ACG}$ (ms)* | *Q-M1 (ms)* | *ΔQ-M1 (ms)* | *IRP (ms)* | *O-H (ms)* | *Q-A2 (ms)* | *ΔQ-A2 (ms)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group 1 : normotensive patients* | | | | | | | | | | | | | |
| 1 | 92 | 95 | −1 | 265 | −6 | 0·36 | 55 | 70 | +9 | 85 | — | 360 | −5 |
| 2 | 80 | 115 | +14 | 300 | +10 | 0·38 | — | 55 | −10 | — | — | 415 | +26 |
| 3 | 87 | 120 | +24 | 250 | −15 | 0·48 | — | — | — | — | — | 370 | +7 |
| 4 | 60 | 95 | −14 | 290 | −32 | 0·33 | 45 | 45 | −26 | — | — | 385 | −44 |
| 5 | 88 | 105 | +7 | 265 | −12 | 0·40 | 70 | 60 | −3 | 80 | 110 | 370 | −3 |
| Mean ±SD | 81 ± 13 | 106 ±11 | +6 ±14 | 274 ± 20 | −11 ±15 | 0·39 ±0·06 | 57 ± 13 | 58 ±10 | −8 ± 15 | 83 | 110 | 380 ± 22 | −4 ± 26 |
| *Group 2 : hypertensive patients* | | | | | | | | | | | | | |
| 6 | 67 | 120 | +16 | 280 | −19 | 0·43 | 50 | 60 | −3 | 95 | 140 | 400 | −5 |
| 7 | 82 | 100 | +2 | 290 | +16 | 0·34 | 40 | 55 | −2 | 65 | 140 | 390 | +16 |
| 8 | 75 | 110 | +7 | 307 | +9 | 0·36 | 55 | 60 | −6 | 130 | 70 | 417 | +18 |
| 9 | 89 | 127 | +32 | 240 | −22 | 0·53 | — | 75 | +21 | — | — | 367 | +8 |
| 10 | 73 | 130 | +28 | 305 | +16 | 0·43 | 75 | 80 | +19 | 130 | 95 | 435 | +61 |
| 11 | 97 | 125 | +33 | 240 | −8 | 0·52 | — | 75 | +24 | — | — | 365 | +23 |
| 12 | 98 | 80 | −12 | 245 | −1 | 0·32 | 50 | 35 | −16 | 80 | 80 | 325 | −25 |
| Mean ±SD | 83 ± 12 | 113 ±18 | +15 ±17 | 272 ± 30 | −1 ± 15 | 0·42 ±0·08 | 54 ± 13 | 63 ±16 | +5 ± 16 | 100 ± 29 | 105 ± 33 | 386 ± 37 | +14 ± 27 |
| *Group 3 : miscellaneous* | | | | | | | | | | | | | |
| 13 | 60 | 125 | +18 | 310 | −1 | 0·40 | 25 | 105 | +39 | 45 | — | 435 | +15 |
| 14 | 63 | 110 | +2 | 275 | −42 | 0·40 | 75 | 50 | −20 | — | — | 385 | −38 |
| Normal value* ±SD | | | 0 ± 11 (F)<br>0 ± 13 (M) | | 0 ± 10 | 0·35 ± 0·04 | 70 ± 16 | | 0 ± 09 (F)<br>0 ± 11 (M) | 67 ± 14 | 99·8 ± 14·2 | | 0 ± 14 |

See text for details of abbreviations and indices; F, female; M, male.

*Weissler, Harris, and Schoenfeld (1968); Kumar and Spodick (1970).

TABLE 3 *Echocardiographic data*

| *Case No.* | *Dd (cm)* | *Ds (cm)* | *%ΔS* | *EDV (ml)* | *ESV (ml)* | *SV (ml)* | *EF (%)* | *CO (l/min)* | *Mean Vpwm (mm/s)* | *Mean Vcf (circ/s)* | *Mitral DCR (mm/s)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group 1 : normotensive patients* | | | | | | | | | | | |
| 1 | — | — | — | — | — | — | — | — | — | — | — |
| 2 | 4·8 | 3·2 | 34 | 112 | 32 | 80 | 71 | 6·4 | 39·3 | 1·13 | 56 |
| 3 | 6·5 | 4·8 | 27 | 275 | 107 | 168 | 61 | 14·9 | — | 1·08 | 160 |
| 4 | — | — | — | — | — | — | — | — | 37·6 | — | — |
| 5 | 4·7 | 3·3 | 31 | 106 | 35 | 71 | 67 | 6·2 | 41·1 | 1·17 | 80 |
| *Group 2 : hypertensive patients* | | | | | | | | | | | |
| 6 | 4·4 | 2·7 | 39 | 85 | 20 | 65 | 76 | 4·4 | 39·3 | 1·38 | 61 |
| 7 | — | — | — | — | — | — | — | — | — | — | 78 |
| 8 | — | — | — | — | — | — | — | — | — | — | — |
| 9 | — | — | — | — | — | — | — | — | — | — | 121 |
| 10 | 5·0 | 3·4 | 32 | 125 | 39 | 86 | 69 | 6·3 | 36·1 | 1·05 | 80 |
| 11 | — | — | — | — | — | — | — | — | — | — | — |
| 12 | 5·8 | 3·8 | 35 | 195 | 55 | 140 | 72 | 14·7 | 68·2 | 1·41 | 130 |
| *Group 3 : miscellaneous* | | | | | | | | | | | |
| 13 | 6·6 | 4·0 | 39 | 287 | 64 | 223 | 78 | 13·4 | 51·6 | 1·27 | 97 |
| 14 | 6·2 | 4·9 | 21 | 238 | 118 | 120 | 50 | 7·6 | 24·4 | 0·76 | — |
| Normal value* ±SD | 4·4 ±0·28 | 2 83 ±0·26 | 35·5 ±3·9 | 86±16 | 23±6 | 63±12 | 73±5 | 4·3±0·8 | | 1·22±0·13 | — |

See text for details of abbreviations and indices.
*McDonald, Feigenbaum, and Chang (1972).

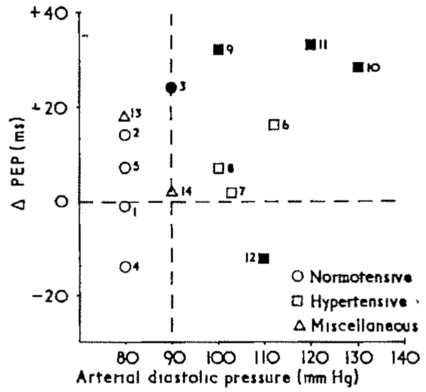

FIG. 2 *Relation between arterial diastolic pressure and ΔPEP. The patients' numbers correspond to those in Table 1 and the solid symbols indicate patients in whom the jugular venous pressure (JVP) was increased. PEP is increased in patients with an increased arterial blood pressure. Patients with fluid overload and an increased jugular venous pressure have the highest diastolic pressures and the greatest ΔPEP.*

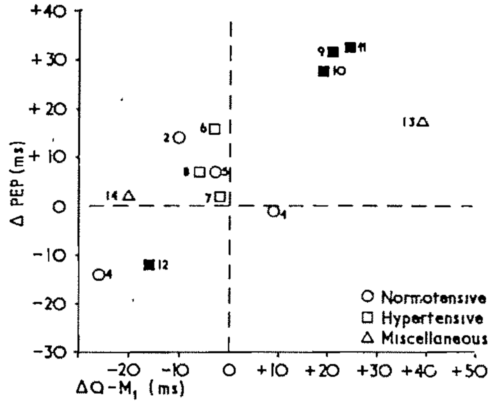

FIG. 3 *Linear relation between ΔQ-M1 and ΔPEP (r=0·77, P<0·01). Case 13 has a great increase in Q-M1 : he did not have an increase in arterial diastolic pressure to account for the prolonged PEP.*

prolonged in the hypertensive group. This finding is in agreement with previous studies in hypertensive patients (Shah and Slodki, 1964).

IRP was normal or increased and the increase was greater in some hypertensive patients. IRP was related to ICT ($r=0{\cdot}73$, $P<0{\cdot}05$). The O-H time (rapid filling period) was normal in most patients but the range was large (70 to 140 ms).

## Echocardiographic studies

The left ventricle was enlarged, especially in patients who had overt volume overload and cardiac failure (Table 4). It contracted well so that measurements of fractional fibre shortening (%ΔS and EF) were normal (Fig. 4). The measurements were slightly decreased in the elderly patient with chronic chest disease (Case 3) and in Case 14 (who was taking propranolol). In 3 patients cardiac output was conspicuously increased. Two of these patients had fluid overload and the signs of cardiac failure (Table 4 and Fig. 5). The other patient (Case 13) was not in cardiac failure at the time of study but had a large hypertrophied heart from previous hypertension and recurrent episodes of fluid overload and cardiac failure. He also had an arteriovenous shunt at the time of study.

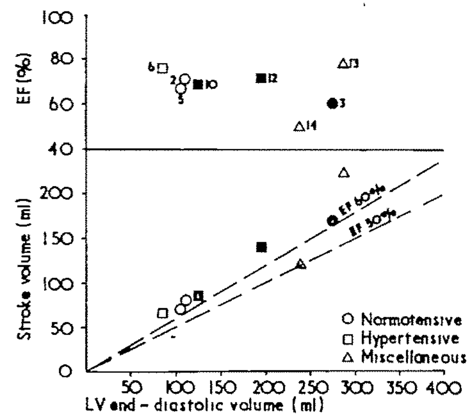

FIG. 4 *Relation between end-diastolic volume (EDV) and stroke volume (SV). Isopleths of ejection fraction (EF) are shown in the lower panel and EF is plotted against EDV in the upper panel. SV increases in patients with a greater EDV so that EF is normal or increased in all patients except patient 14, who was taking propranolol. Solid symbols are used for patients with a raised jugular venous pressure.*

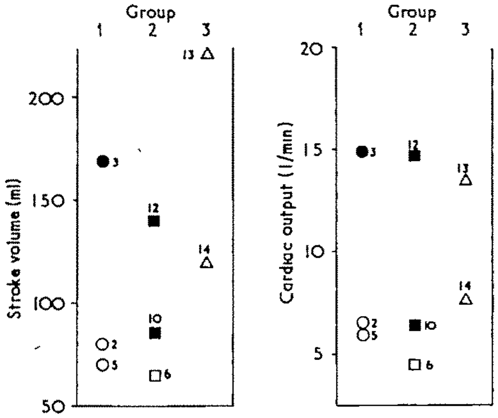

FIG. 5 *Stroke volume and cardiac output in the 3 groups. Stroke volume and cardiac output are greatly increased in Cases 3 and 12 (who had severe fluid overload and an increased jugular venous pressure) and in Case 13, who had severe fluid overload and previous hypertension but normal jugular venous pressure at the time of study following haemodialysis.*

TABLE 4 *Echocardiographic data in relation to clinical right heart failure*

| *Case No.* | *Dd (cm)* | *Ds (cm)* | *%ΔS* | *EF (%)* | *Echo SV (ml)* | *CO (l/min)* | *Mean Vcf (circ/s)* | *Mitral DCR (mm/s)* |
|---|---|---|---|---|---|---|---|---|
| *Group A: normal JVP* | | | | | | | | |
| 2 | 4·8 | 3·2 | 34 | 71 | 80 | 6·4 | 1·13 | 56 |
| 5 | 4·7 | 3·3 | 31 | 67 | 71 | 6·2 | 1·17 | 80 |
| 6 | 4·4 | 2·7 | 39 | 76 | 65 | 4·4 | 1·38 | 61 |
| 7 | — | — | — | — | — | — | — | 78 |
| *Group B: increased JVP* | | | | | | | | |
| 3 | 6·5 | 4·8 | 27 | 61 | 168 | 14·9 | 1·08 | 160 |
| 10 | 5·0 | 3·4 | 32 | 69 | 86 | 6·3 | 1·05 | 80 |
| 12 | 5·8 | 3·8 | 35 | 72 | 140 | 14·7 | 1·41 | 130 |
| Normal value* ±SD | 4·40 ±0·28 | 2·83 ±0·26 | 35·5 ±3·9 | 73 ±5 | 63 ±12 | 4·3 ±0·8 | 1·22 ±0·13 | — |

See text for details of abbreviations and indices.
*McDonald, Feigenbaum, and Chang (1972).

The velocity measurements mean Vcf and mean Vpwm were normal except in Case 14, who was taking propranolol (Table 3, Fig. 6).

The mitral diastolic closure rate was normal or increased. It was increased in patients who had a large stroke volume ($r=0{\cdot}97$, $P<0{\cdot}01$), except in Case 13, who had a relatively low mitral diastolic closure rate (Fig. 7). This may reflect an abnormality of ventricular compliance in this patient and may explain his recurrent episodes of cardiac failure. Mitral diastolic closure rate was also related to rapid filling period (O-H time): patients with a large stroke volume and an increased mitral diastolic closure rate had rapid ventricular filling in early diastole and a short O-H time ($r=-0{\cdot}80$, $P>0{\cdot}05$).

### Serial study

Case 12 presented with severe uraemia which had not been treated. He was ill with hypertension, anaemia, fluid overload, tachycardia, and a raised jugular venous pressure. He had a large stroke volume and cardiac output with a large left ventricular end-diastolic volume. The left ventricle contracted very well (%ΔS 35%; mean Vcf 1·41 circ/s; ejection fraction 72%) (Fig. 8).

Three hours after peritoneal dialysis arterial blood pressure was unchanged. He had lost 4 kg in weight and the left ventricular end-diastolic volume, left atrial volume, and aortic root diameter were smaller. Stroke volume decreased and cardiac output was maintained by reflex tachycardia. He was slightly volume-depleted. There was also a change in measurements of left ventricular function with a small decrease in mean Vcf, mean Vpwm, and ejection fraction, as a result of the operation Starling's law. The systolic time intervals reflected these changes: PEP increased, ΔLVET decreased, and the PEP/LVET ratio was higher, after dialysis (Fig. 8).

### Discussion

There are several studies of circulatory dynamics in renal failure (Agrest and Finkielman, 1967; Gibson, 1966; Del Greco *et al.*, 1969; Neff *et al.*, 1971) and different mechanisms have been suggested to explain the abnormal findings. There is an increased volume and pressure load on the left ventricle, there may be pericardial disease, and there may be additional coronary artery disease (Lewin and Trautman, 1971; Popowniak, Nakamoto, and Shaldon, 1975). In addition, myocardial performance may be altered by electrolyte disturbances or by a specific toxic substance with myocardial depressant action. Animal experiments in guinea-pigs, frogs, and rabbits (Raab, 1944) and in isolated rat heart preparations provide evidence for a cardiac depressant effect of uraemic serum (Prosser and Parsons, 1975; Hennemann *et al.*, 1975). Dietary factors may be important (Bailey, Hampers, and Merrill, 1967) and Gotloib and Servadio (1975) have reported a patient in whom chronic haemodialysis was complicated by beriberi heart failure. Pathological changes are frequent

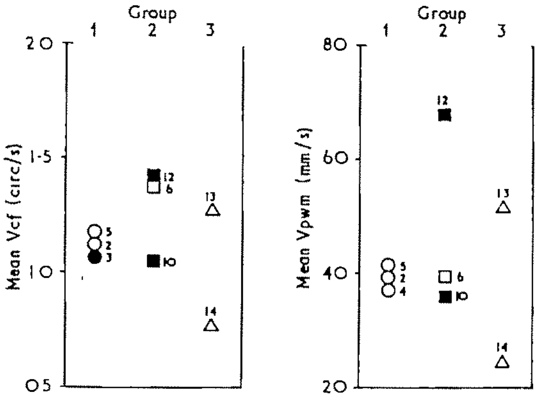

FIG. 6 *Velocity measurements of left ventricular function. Mean Vcf and Vpwm are normal or increased in all patients except Case 14, who was taking propranolol.*

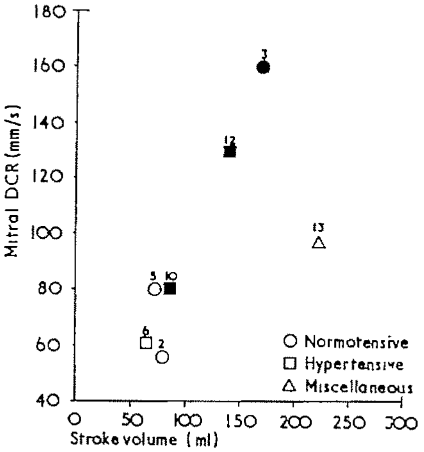

FIG. 7 *Linear relation between stroke volume (SV) and mitral diastolic closure rate (DCR) ($r=0{\cdot}97$, $P<0{\cdot}01$). In Case 13 the DCR is not increased despite the high SV.*

in the myocardium of patients with the uraemic syndrome (Langendorf and Pirani, 1947). However, cardiac output and cardiac performance are enhanced in some animals with acute and short-term chronic renal failure (Knowlan, Piatnek, and Olson, 1961; Penpargkul and Scheuer, 1972).

There are no detailed studies of left ventricular function in patients with uraemia. Newmark and Kohn (1974) showed a change in STI measurements after renal transplantation and they interpreted this as showing an improvement in myocardial performance. Bornstein *et al.* (1975) studied a group of patients before and immediately after dialysis using STI and showed that PEP increased while LVET and ΔLVET decreased: this was attributed to a Starling effect, with or without a change in myocardial contractility. The serial study on our patient confirms their findings. Other published reports suggest the syndrome of uraemic cardiomyopathy, but on the basis of clinical findings alone without left ventricular function studies (Ianhez, Lowen, and Sabbaga, 1975).

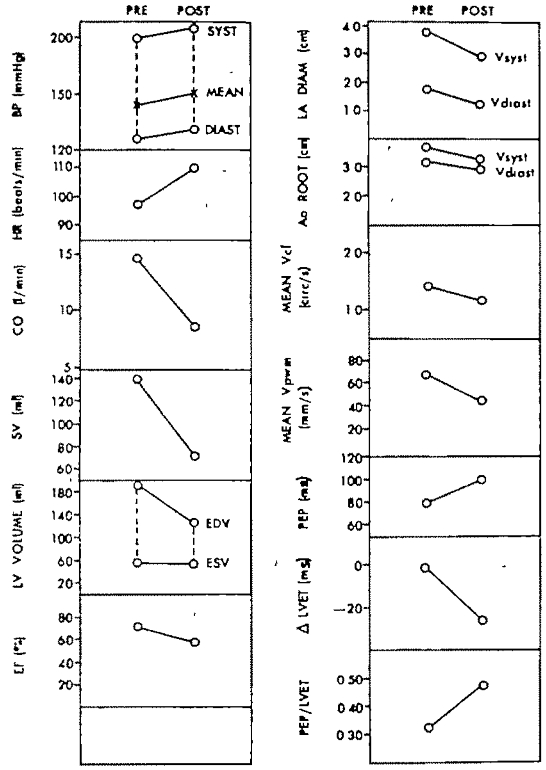

FIG. 8 *Serial study in Case 12 before (pre) and 3 hours after (post) peritoneal dialysis. There is little change in arterial blood pressure (BP). All measurements of cardiac volume are smaller after dialysis (LV end-diastolic volume, left atrial diameter, and the aortic root diameter). Stroke volume (SV) and the velocity measurements of LV function (mean Vcf and Vpwm) decrease by operation of the Starling effect. Cardiac output (CO) falls and there is reflex tachycardia. These changes are reflected in the systolic time intervals: there is an increase in PEP, a decrease in LVET, and an increase in the PEP/LVET ratio after dialysis. V syst=ventricular systole; V diast=ventricular diastole.*

The present study provides no evidence for the existence of a specific uraemic cardiomyopathy. On the contrary, systolic function of the left ventricle is normal, even in patients who are severely uraemic, hypertensive, fluid-overloaded, and anaemic, clinically ill and with the physical signs of cardiac failure. The heart is enlarged but myocardial performance is normal as measured by % ΔS, ejection fraction, and mean Vcf so that stroke volume and cardiac output are increased as a result of operation of the Starling mechanism. It is possible that more sensitive techniques for assessing left ventricular performance may show that the response to the loading conditions is normal but suboptimal in chronic renal failure; we have not studied the patients during and after exercise since many of them were very ill. None the less, overall left ventricular function is normal at rest and it seems that a 'myocardial factor' is not important clinically in the pathogenesis of cardiac failure in uraemia unless additional cardiac disease (e.g. coronary artery disease) is present.

It should be noted that STI measurements must be interpreted carefully in patients who have abnormal loading conditions (Karnegis and Wang, 1961; Talley, Meyer, and McNay, 1971). Despite normal echocardiographic measurements, PEP is prolonged in some of our patients and the PEP/LVET ratio is increased. This does not necessarily indicate an alteration in myocardial contractility since preload and afterload are abnormal; ΔPEP is related to arterial diastolic pressure and to ΔQ-M1, supporting this view. A similar discrepancy has been seen in patients with chronic obstructive pulmonary disease, who have abnormal STI measurements but normal LV systolic function as measured by more direct techniques (Unger *et al.*, 1975).

Left ventricular compliance is normal in early diastole, and the mitral diastolic closure rate increases appropriately in patients who are fluid-overloaded with a large stroke volume. The patient studied after renal transplantation (Case 13) had a disproportionately slow mitral diastolic closure rate despite a large stroke volume. This suggests that he had abnormal ventricular compliance and may explain recurrent episodes of cardiac failure for which he was treated with digitalis. The cause of this altered compliance is uncertain. There was a long history of fluid overload and hypertension (though these were controlled by drugs at the time of study). The patient died subsequently and necropsy was performed. The left ventricle was greatly hypertrophied and dilated; the severe left ventricular hypertrophy may explain the decreased ventricular compliance (Grossman *et al.*, 1974). Systolic function had been adequate despite the abnormal loading conditions.

In summary, left ventricular performance was normal both in systole and diastole in all but 2 of our patients. One (Case 14) had a slight decrease in systolic left ventricular function and this was thought to be the effect of propranolol in a patient dependent on sympathetic compensatory mechanisms to maintain normal haemodynamics. The other (Case 13) had good systolic function but altered diastolic compliance of the left ventricle, probably caused by severe left ventricular hypertrophy. Several other patients were extremely ill with uraemia, hypertension, and fluid overload at the time of study, but in all of these left ventricular function was good. It seems that uraemia itself is not associated with myocardial dysfunction.

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# Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combination of beta-receptor blocking and vasodilator agent

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*Systemic and pulmonary haemodynamics were studied at rest in the supine and upright position, and during exercise in the sitting position at 75 and 150 Watt, in 13 hypertensive men aged 50·8±8·7 years before and after 13 months treatment with oral oxprenolol (120 to 160 mg t.i.d.) supplemented by oral hydrallazine (50 to 75 mg t.i.d.) during the last 6 months. Pressures were recorded by means of catheters inserted percutaneously into the pulmonary and brachial artery; cardiac output was determined according to Fick.*

*Treatment resulted in a significant reduction of systemic systolic, diastolic, and mean pressures at rest in the supine position and during exercise, and of systolic pressures in the upright posture. Pulmonary systolic and mean pressures increased slightly at rest in the supine position and during exercise, and no changes occurred at rest in the upright position. The left ventricular filling pressure was unchanged at rest both in the supine and upright position; it increased slightly during exercise.*

*The haemodynamic changes by which systemic pressure was reduced were those typical of beta-adrenergic blockade: reduction of cardiac output resulting from a decrease of both heart rate and stroke volume, while the total systemic vascular resistance was unchanged at rest in the supine position but increased in the upright posture and during exercise. The A-V $O_2$ difference increased remarkably.*

*This long-term observation again suggests that the acute haemodynamic effects of an antihypertensive regimen can be modified during long-term application. It did not give evidence of a readjustment of the vascular resistance occurring, at least not in the upright position and during exercise, as has been suggested for long-term beta-adrenergic blockade.*

Adrenergic beta-receptor blocking agents have increasingly been used in the treatment of hypertensive disease during the past years (Prichard and Gillam, 1966, 1969; Dollery, Paterson, and Conolly, 1969; Johnsson *et al.*, 1969; Werkö, 1971; Eisalo *et al.*, 1974; Bengtsson, 1974; Hansson and Werkö, 1975, and others). Their blood pressure lowering action is associated with a fall in cardiac output; the systemic vascular resistance is initially not consistently affected (Sannerstedt, 1974), but may be reduced during prolonged treatment (Tarazi and Dustan, 1972).

Advanced stages of hypertension are associated with low cardiac output and increased systemic vascular resistance (Lund-Johansen, 1967). Because of their haemodynamic effects beta-receptor blocking agents evidently are not the drugs of choice from the physiological point of view in such conditions. On the other hand, peripheral vasodilators lower systemic blood pressure by decreasing the systemic vascular resistance (Åblad, 1963; Johnston, 1975; Zacest, 1975). However, the pressure decrease activates the homeostatic mechanism of the baroreceptors, thus causing an increase in heart rate and cardiac output. This secondary effect has in the past limited the usefulness of vasodilators as antihypertensive agents.

Studies in both the experimental animal (Brunner, Hedwall, and Meier, 1967) and man

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(Sannerstedt *et al.*, 1971) have shown that the homeostatic reflex mechanism elicited by the vasodilator hydrallazine can be counteracted by simultaneous administration of a beta-receptor blocking agent; and several clinical trials have documented the beneficial effect of such combined treatment (Katila and Frick, 1970; Berglund and Hansson, 1971; Žacest, Gilmore, and Koch-Weser, 1972; Freeman and Knight, 1975).

However, in spite of the evident rationale for combined beta-receptor blocking and vasodilator treatment, at least in certain stages of the hypertensive disease, information concerning the haemodynamic effects of such therapy is extremely scanty. There appears to be but a single study of its acute effects (Sannerstedt *et al.*, 1971), while there is no information regarding the haemodynamic adaptation to long-term treatment. The purpose of the present study was to provide such information. It is exclusively focused on the haemodynamic effects, while further clinical evaluations and renal effects will be reported elsewhere. The beta-receptor blocking and vasodilator agents used were oxprenolol (Trasicor) and hydrallazine (Apresoline), respectively. Oxprenolol was given alone during an average period of 7 months; thereafter hydrallazine was added, the combined treatment lasting another 6 months.

## Patients

Sixteen hypertensive patients (15 men, one woman) who were referred to the department for investigation of cardiac and/or renal function gave their informed consent to this study; after taking part in the initial investigation, 3 of them, however, did not attend the follow-up examinations regularly and were withdrawn.

Thirteen male patients, mean age 50·8±8·7, range 35·4 to 64·2 years, completed the entire trial. In 5 of them hypertension had been discovered recently and no treatment had been initiated: 8 of them had suffered from hypertension for between 5 and 12 years and had been receiving antihypertensive treatment. In all patients, however, antihypertensive therapy had been discontinued at least 6 weeks before the initial examination. Blood pressures when measured by the Riva-Rocci cuff method ranged between 155/105 and 210/120 mmHg at rest and between 210/115 and 270/140 mmHg during exercise. The clinical evaluation indicated that all had stage 1 to 2 essential hypertension using criteria described by the W.H.O. (1959); blood counts, serum electrolytes, serum creatinine, liver and renal function tests were normal. Fundoscopic examination revealed no abnormality in 5 subjects; 8 had non-exudative hypertensive changes, grade 1 to 2 of the Keith-Wagener-Barker scale. None had evidence of ischaemic heart disease as evaluated by exercise electrocardiogram (maximal work load 150 Watts in 7 and 200 Watts in 6 subjects) or of significant cardiac enlargement (mean relative heart volume 475±81, range 370 to 635 $ml/m^2$ body surface area). Chest *x*-ray films and spirometry gave no indication of lung disease. Some relevant anthropometric data including blood volume, heart volume, and total amount of haemoglobin are given in Table 1.

TABLE 1

| | *Mean* | *SD* | $\bar{D}$ | $\bar{D}$% |
|---|---|---|---|---|
| Age (ys) | 50·8 | 8·7 | 1·1 | 2·0 |
| Weight (kg) | 83·2 | 8 1 | 2·1** | 2 5** |
| Blood volume (l) | 6·5 | 1·1 | 0 7 | 10·8 |
| Total Hb (g) | 908 | 166 | 21 | 2 3 |
| Heart volume (ml)† | 965 | 184 | 59 | 6 1 |

Means and standard deviations (SD) of some anthropometric data before and their mean ($\bar{D}$) and percentage ($\bar{D}$%) changes after a 13-month period of treatment. Asterisks denote level of statistical significance: **=P<0 01.
†Determined by Larsson and Kjellberg (1948).

## Methods

### General procedure

The patients were studied with identical techniques and under identical conditions before and after treatment with the combination of oxprenolol plus hydrallazine.

The entire *investigation programme* comprised a complete clinical evaluation including blood and urine analysis, a chest *x*-ray film, spirometry, an exercise test with simultaneous electrocardiogram and blood pressure (cuff method) recording (Jacobsson *et al.*, 1966), inulin- and PAH-clearance, determination of blood volume and renin activity, and the haemodynamic investigation.

The *antihypertensive treatment* aimed at reaching blood pressure levels at rest below 140/90 mmHg when measured by the Riva Rocci method and during exercise at the highest load below 220/100 mmHg. Therapy was started within 4 weeks after the initial series of examinations with 40 mg t.i.d. of oral oxprenolol. This dose was gradually increased by increments of 40 mg t.i.d. up to 160 mg t.i.d. or until the maximal blood pressure lowering effect was attained. Mean duration of treatment with oxprenolol as the only drug was 7 months, all patients being on a total daily dose of 360 or 480 mg oxprenolol at the end of this period.

After a new series of examinations comprising the above-mentioned tests but excluding the haemodynamic study, oral hydrallazine was added in an initial dose of 25 mg t.i.d. and gradually increased to a maximum 75 mg t.i.d. until the desired blood pressure level or the maximal pressure lowering effect was achieved. All patients were finally on a total daily dose of 150 or 225 mg hydrallazine.

### Haemodynamic investigation

Haemodynamics were studied at rest in the supine and in the upright position, and during exercise at two different work loads in the sitting position, on an electrically braked bicycle ergometer (Jacobsson *et al.*, 1966). Both the orthostatic test and exercise on each work load lasted for 6 minutes. Work loads were 75 ($W_1$) and 150 Watt ($W_2$), the higher one corresponding to about 70 to 80 per cent of the patient's maximal $O_2$ uptake.

Having fasted overnight the patients came to the laboratory at about 8 a.m. Polyvinyl catheters were inserted percutaneously (Koch, 1971a) in a brachial artery (the same on both occasions) and in an antecubital vein; the tip of the venous catheter was then placed into the main pulmonary artery using a spiral guide wire and fluoroscopy; 20 minutes were allowed to elapse before measurements were started.

Blood pressures were recorded by means of an Elema 82 multichannel direct recorder using the Elema strain gauge transducers, together with the electrocardiogram. In the supine position the mid-axillary line, and in the erect and sitting position the sternal angle were taken as zero pressure levels. Pressure recordings were taken after 4 minutes' standing and exercise, respectively.

Cardiac output was determined according to the direct Fick principle. Oxygen uptake was measured using the Douglas bag technique. Expired air was collected during 5 minutes at rest in the supine and during 3 minutes at rest in the erect posture and during exercise, starting 3 minutes after the onset of standing and exercise, respectively. Arterial and mixed venous blood samples were taken simultaneously during the collection of expired air.

The systemic (peripheral) vascular resistance (SVR) and the pulmonary vascular resistance (PVR) were calculated according to the equations:

$$\mathrm{SVR} = \frac{\bar{P}_{BA} - \bar{P}_{RA}}{\mathrm{CO}} \text{ and}$$

$$\mathrm{PVR} = \frac{\bar{P}_{PA} - \bar{P}_{\mathrm{diast.}\,PA}}{\mathrm{CO}}$$

where $\bar{P}_{BA}$, $\bar{P}_{RA}$, and $\bar{P}_{PA}$ are the mean pressures in the brachial artery, right atrium (resting value), and pulmonary artery, respectively, and $\bar{P}_{\mathrm{diast.}\,PA}$ is the diastolic pressure in the pulmonary artery. It is well established (Forsberg, 1971) that the pulmonary artery diastolic pressure reflects the pulmonary wedge pressure provided there is no significant rise in pulmonary vascular resistance.

### Blood and gas analyses

The volume of expired air was measured in a gasometer, $O_2$ and $CO_2$ were determined according to Scholander (1947), the $O_2$ saturation and the haemoglobin concentration with a spectrophotometric method (Holmgren and Pernow, 1959) using a Beckman B photometer; *p*H, $P_{O_2}$, and $P_{CO_2}$ were determined with microelectrodes using Radiometer's PMH 72, lactic acid was determined enzymatically (Hohorst, 1963). Blood gas analyses were performed within 30 minutes after sampling. Methodological details, including the analytical accuracy, are given elsewhere (Koch, 1968).

### Statistical methods

Current statistical methods were used for calculation of standard deviations (SD), mean differences ($\bar{D}$), and t-analyses (Snedecor, 1967). Comparison of data obtained before and after treatment was always based on paired samples.

## Results

Mean values and standard deviations of some relevant haemodynamic measurements before the onset of treatment, as well as the changes observed after the combined oxprenolol-hydrallazine treatment, are given in Tables 2 and 3.

The pretreatment average *systemic blood pressure* was 159/88 mmHg, mean 117 mmHg, at rest in the supine, and 165/100 mmHg, mean 125 mmHg, in the upright position; it rose to 248/113 mmHg, mean 160 mmHg, during exercise ($W_2$). Treatment resulted in significantly lower blood pressure levels under all conditions, the effect being most pronounced during exercise and systolic pressures being most affected. Though the average diastolic and mean pressures during standing were about 10 per cent lower, this difference was just below the limit of statistical significance.

*Blood pressures in the pulmonary circulation* were within normal limits both before and after treatment; after treatment, however, they were slightly ($P < 0.05$ to $P < 0.001$) higher during exercise and at rest in the supine position. The effect was most pronounced during exercise.

*Heart rate* was significantly lower after treatment

TABLE 2

| | | *Mean* | *SD* | $\bar{D}$ | $\bar{D}\%$ |
|---|---|---|---|---|---|
| *Brachial artery* | | | | | |
| Systolic pressure (mmHg) | R | 159 | 19 | −23*** | −14·6*** |
| | O | 165 | 24 | −20** | −12·0** |
| | $W_1$ | 205 | 27 | −38*** | −18·5*** |
| | $W_2$ | 248 | 33 | −68*** | −27·3*** |
| Diast. pressure (mmHg) | R | 88 | 10 | −8* | −8·9* |
| | O | 100 | 15 | −9 | −9·2 |
| | $W_1$ | 102 | 12 | −10** | −10·2** |
| | $W_2$ | 113 | 16 | −21*** | −18 4*** |
| Mean pressure (mmHg) | R | 117 | 13 | −14** | −12·0** |
| | O | 125 | 18 | −12 | −9·7 |
| | $W_1$ | 141 | 15 | −19** | −13·4** |
| | $W_2$ | 160 | 21 | −29*** | −18 4*** |
| *Pulmonary artery* | | | | | |
| Systolic pressure (mmHg) | R | 24 | 3 | 3* | 14·2* |
| | O | 22 | 5 | 1 | 3 7 |
| | $W_1$ | 38 | 8 | 6*** | 14 5*** |
| | $W_2$ | 46 | 8 | 6** | 14 2** |
| Diastolic pressure (mmHg) | R | 7 | 3 | 1 | 22 1 |
| | O | 7 | 3 | 0 | 3·1 |
| | $W_1$ | 12 | 5 | 4** | 36·9** |
| | $W_2$ | 14 | 6 | 7*** | 51·0*** |
| Mean pressure (mmHg) | R | 13 | 3 | 3* | 22·7* |
| | O | 11 | 3 | 1 | 13 0 |
| | $W_1$ | 21 | 6 | 7*** | 34·6*** |
| | $W_2$ | 28 | 7 | 8*** | 28·4*** |
| *Periph. vasc. resist* (mmHg/l per min) | R | 14 8 | 3·4 | 3·4 | 23 0 |
| | O | 18·4 | 5 8 | 8 3* | 45 1* |
| | $W_1$ | 8 9 | 2 2 | 4·7** | 52·8** |
| | $W_2$ | 7·4 | 1·1 | 2·6** | 35·1** |
| *Pulm. vasc. resist.* (mmHg/l per min) | R | 0·74 | 0·25 | 0·58*** | 78·4*** |
| | O | 0 76 | 0 41 | 0 94** | 123·7** |
| | $W_1$ | 0·60 | 0 15 | 0·87*** | 145·0*** |
| | $W_2$ | 0·62 | 0 19 | 0·57*** | 91 9*** |

Means and standard deviations (SD) of blood pressures and vascular resistances before and their mean ($\bar{D}$) and percentage ($\bar{D}\%$) changes after 13 months of antihypertensive treatment at rest in the supine (R) and the upright (O) position and during exercise at two different work loads ($W_1$=75 W, $W_2$=150 W). Asterisks denote level of statistical significance: *=P<0 05, **=P<0 01, ***=P<0 001.

TABLE 3

| | | *Mean* | *SD* | $\bar{D}$ | $\bar{D}\%$ |
|---|---|---|---|---|---|
| Heart rate | R | 71 | 12 | −8 | −11 3 |
| | O | 80 | 15 | −14* | −17 5* |
| | $W_1$ | 107 | 12 | −19*** | −17·8*** |
| | $W_2$ | 151 | 16 | −36*** | −23 8*** |
| $\dot{V}_E$ (l/min BTPS) | R | 17·9 | 7 1 | −2 6 | −14 5 |
| | O | 21·3 | 9·4 | −4·5* | −21 1* |
| | $W_1$ | 49 6 | 7 8 | −5·7* | −11 5* |
| | $W_2$ | 87·7 | 26·0 | −2 8 | −3 2 |
| $V_{O_2}$ (l/min STPD) | R | 0 31 | 0·04 | −0 01 | −3 2 |
| | O | 0 37 | 0·08 | −0 06* | −16 2* |
| | $W_1$ | 1 19 | 0 15 | −0 06 | −5 0 |
| | $W_2$ | 1 97 | 0·17 | 0 11 | 5 6 |
| $AVO_2$ diff. (ml/l) | R | 39 3 | 7·2 | 10 3** | 26 2** |
| | O | 53 4 | 11·9 | 22 7*** | 42 5*** |
| | $W_1$ | 76·4 | 18·2 | 49 7*** | 65 1*** |
| | $W_2$ | 94 3 | 23·5 | 61·7*** | 65 4*** |
| CO (l/min) | R | 8 7 | 1·9 | −2 0** | −23·4** |
| | O | 7 2 | 2·1 | −2·7** | −38 0** |
| | $W_1$ | 16·2 | 3 6 | −7 1*** | −43 8*** |
| | $W_2$ | 21 6 | 4 0 | −8 5*** | −39 4*** |
| SV (ml) | R | 116 | 30 | −19* | −16 4* |
| | O | 91 | 22 | −22* | −24 2* |
| | $W_1$ | 151 | 27 | −46** | −30·5** |
| | $W_2$ | 145 | 33 | −28** | −19 3** |
| Lactate (mmol/l) | R | 0·98 | 0 44 | 0 12 | 12 2 |
| | O | 0·96 | 0·42 | 0·19 | 19·8 |
| | $W_1$ | 2 06 | 0 71 | 0 65 | 31 6 |
| | $W_2$ | 4·19 | 1·66 | 0 92** | 22 0** |

Means and standard deviations (SD) of some circulatory and respiratory variables before and their mean ($\bar{D}$) and percentage ($\bar{D}\%$) changes after 13 months of antihypertensive treatment at rest in supine (R) and upright (O) position and during exercise at two different work loads ($W_1$=75 W, $W_2$=150 W). Asterisks denote level of statistical significance: *=P<0 05, **=P<0·01, ***=P<0 001.

at rest in the upright position (17%, $P < 0{\cdot}05$) and during exercise (18% and 24%, $P < 0{\cdot}001$, at $W_1$ and $W_2$, respectively); it was on the average 8 beats lower in the supine position ($0{\cdot}1 > P < 0{\cdot}05$).

Both *oxygen uptake* ($\dot{V}_{O_2}$) *and minute ventilation* ($\dot{V}_E$) were lower in the upright position after treatment ($P < 0{\cdot}05$), the minute ventilation was also lower during $W_1$ ($P < 0{\cdot}05$).

Pretreatment *cardiac output* both at rest and during exercise was high ($8{\cdot}7 \pm 1{\cdot}9$ l/min at rest and $21{\cdot}6 \pm 4{\cdot}0$ l/min at $W_2$ corresponding to an oxygen uptake of 2 l/min) particularly when the patients' age is taken into account. Post-treatment cardiac outputs were significantly lower, the decrease ranging between 23 per cent at rest in the supine $P < 0{\cdot}01$) and about 40 per cent in the erect position and during exercise ($P < 0{\cdot}001$). This was partly the result of a similar decrease of the *stroke volume* ranging between 16 per cent at rest and 30 per cent during exercise ($W_2$). The relative decrease in both cardiac output and stroke volume was most pronounced during exercise at the lower level.

Inversely to the changes of cardiac output the *arterio-mixed venous oxygen difference* was much higher after treatment, the increase ranging between 26 per cent ($P < 0{\cdot}01$) at rest and 65 per cent ($P < 0{\cdot}001$) during exercise.

Both before and after treatment total *systemic vascular resistance* was only slightly raised in comparison with normotensives; after treatment, it was not significantly changed at rest in the supine, but higher in the upright position (45%, $P < 0{\cdot}05$) and during exercise (53 and 35%, $P < 0{\cdot}01$, at $W_1$ and $W_2$, respectively). Post-treatment *pulmonary vascular resistance* was higher under all conditions.

There was a general tendency towards higher *arterial lactic acid concentrations* after treatment; the increase being about 20 per cent during $W_2$ ($P < 0{\cdot}01$).

## Discussion

Treatment with oxprenolol for an average duration of 13 months, supplemented by hydrallazine during the last 6 months, had a distinct antihypertensive effect both at rest and during exercise, inducing a fall in arterial mean pressures by 14 mmHg at rest and by 19 and 29 mmHg during exercise at loads $W_1$ (oxygen uptake $1{\cdot}2 \pm 0{\cdot}2$ l/min) and $W_2$ (oxygen uptake $2{\cdot}0 \pm 0{\cdot}2$ l/min) respectively. In the erect posture the average systolic pressure was 20 mmHg lower after treatment; the decreases observed in mean and diastolic pressures were at borderline statistical significance.

The mode of antihypertensive action was similar at rest and during exercise: blood pressure was lowered by a reduction of cardiac output, while the systemic vascular resistance was mainly unchanged at rest in the supine position, but higher in the upright posture and during exercise. The relative reduction of cardiac output was most pronounced during work at the lower load ($W_1$) at which it corresponded to 44 per cent of the pretreatment level. Both a decrease of stroke volume by maximally 30 per cent ($W_1$) and of heart rate by maximally 24 per cent ($W_2$) contributed to the reduction of cardiac output. These changes towards a more hypokinetic pattern of circulation were accompanied by a significant increase of the arterio-mixed venous oxygen (A-$\bar{V}$ $O_2$) difference. During exercise at load $W_2$ the A-$\bar{V}$ $O_2$ difference rose from 94 to as much as 155 ml $O_2$/l blood. This type of haemodynamic adaptation is typical of that observed during the action of adrenergic beta-receptor blockers; it has also been reported for other agents interfering with sympathetic nervous activity, such as clonidine (Koch, 1971b) which mainly inhibits the sympathetic vasomotor centre, or the ganglion blocking agent guanethidine (Sannerstedt and Conway, 1970).

Haemodynamic observations after prolonged treatment with adrenergic beta blocker agents are, however, scanty and mainly confined to resting conditions and relatively short periods; in only one study did duration of treatment apparently exceed 12 months (Tarazi and Dustan, 1972). While all studies have shown the typical reduction of heart rate, blood pressure, stroke volume, and cardiac output and the increase of the A-$\bar{V}$ $O_2$ difference (Frohlich *et al.*, 1968; Eisalo, Luomanmäki, and Heikkilä, 1969; Taylor *et al.*, 1970; Majid *et al.*, 1970; Sannerstedt *et al.*, 1972; Tarazi and Dustan, 1972; Hansson *et al.*, 1974), the results are contradictory with respect to the effect on systemic vascular resistance. Vascular resistance regularly increases in the acute experiment and in the early stage of treatment with a beta-receptor blocking agent (Sannerstedt, 1974). While earlier observations indicated that this rise in resistance persisted during long-term treatment (Frohlich *et al.*, 1968), recent findings suggest that it may return to initial or even lower levels during prolonged treatment in spite of sustained reduction of blood pressure and cardiac output (Tarazi and Dustan, 1972; Hansson *et al.*, 1974). Resetting of the baroreceptors in response to chronic reduction of cardiac output (Tarazi and Dustan, 1972) and/or adaptation changes in the blood vessel calibre (Brunner, 1974) have been thought to be responsible for this change in vascular resistance. In the present study, systemic vascular resistance increased in 9 and decreased in 4 patients at rest in the recumbent position, but it increased in all patients in the upright posture and during exercise. Despite a drastic reduction of cardiac output and a duration of treatment exceeding one year, and in spite of the additional use of the vasodilator hydrallazine, the results of the present study thus do not give evidence of such a readjustment of the vascular resistance occurring, at least not as far as conditions at rest in the erect posture and during exercise are concerned.

The patients included in the present study corresponded mainly to stage 1 to 2 hypertension according to the W.H.O. classification (1959); roughly 50 per cent of them were only moderately hypertensive and their pretreatment cardiac outputs showed a surprisingly hyperkinetic pattern of circulation: $8{\cdot}7 \pm 1{\cdot}7$ and $21{\cdot}6 \pm 4{\cdot}0$ l/min corresponding to cardiac indices of $4{\cdot}0 \pm 0{\cdot}9$ and $10{\cdot}7 \pm 2{\cdot}0$ l/min $\times m^2$ at rest and during $W_2$, respectively. Correspondingly, their A-$\bar{V}$ $O_2$ differences were low, and the systemic vascular resistance was only moderately raised. This degree of hyperdynamic circulation is unusual for hypertensives of this age group and has probably largely contributed to the pronounced effects of treatment observed on cardiac output, the A-$\bar{V}$ $O_2$ difference and on the calculated vascular resistance. It is established that the cardiac output lowering effect of beta-receptor blockade is most pronounced in hyperkinetic states (Sannerstedt, 1974).

However, the degree of reduction of cardiac output in the present study is still more surprising in view of the additional treatment with the peripheral vasodilator hydrallazine. From acute experiments (Brunner *et al.*, 1967; Sannerstedt *et al.*, 1971, 1972) one should expect an attenuation or reversal of the cardiac output reducing effect and a decrease of vascular resistance. Using a dye dilution technique, Sannerstedt (1974) actually found this trend of haemodynamic readjustment after addition of hydrallazine to alprenolol in 3 hypertensive patients at rest; treatment with alprenolol had lasted for one month and combined treatment with additional hydrallazine for another 2 to 5 months. The results obtained in the present study at rest in the supine position are consistent with these observations, but the data obtained in the upright posture and particularly during exercise suggest that the vasodilator haemodynamic action of hydrallazine under these conditions is highly, if not entirely, overshadowed by that of the beta-receptor blocking agent. This simply implies that the beta-receptor blockade obtained with the dose of oxprenolol was efficient enough not only to control the hyperdynamic circulation of these patients but also to inhibit the hydrallazine-induced baroreflex mechanism.

Our knowledge of the effect of antihypertensive drugs on the pulmonary circulation is still more limited. It is generally agreed that alpha- and beta-receptor mediated vasomotor effects do not play a substantial role in the regulation of the pulmonary circulation and that pressure changes in the systemic arterial circulation have very little effect on the low pressure system of the pulmonary circulation (Gauer, 1972). In the present study pulmonary arterial pressures rose slightly at rest in the recumbent position and during exercise, and were unchanged in the upright position. Because of the substantial reduction of cardiac output, however, the calculated pulmonary vascular resistance was higher in all instances. These findings are at variance with the observation of insignificantly changed pulmonary pressures and resistances at rest and during moderate exercise after a 12-week oral administration of oxprenolol in the series of Taylor *et al.* (1970). However, this discrepancy might be entirely the result of the small number of patients (6) in the latter series. Clonidine (Koch, 1971b), which apparently inhibits the sympathetic vasomotor centre, and AH 5158, a combined alpha- and beta-receptor blocking agent (Koch, 1976), lacked the pressure raising effect on the pulmonary circulation at least in the acute experiment.

The pulmonary artery diastolic pressure has been shown (Forsberg, 1971) to reflect pulmonary wedge and thus left ventricular filling pressures in the absence of significant increases in pulmonary vascular resistance. Though the use of left ventricular filling pressure as a method of evaluating myocardial contractility is crude and insensitive, the absence of any pressure rise at rest both in the recumbent and the erect posture suggests that oxprenolol, at least in the combination with hydrallazine lacks significant negative inotropic effects at rest; but this effect is measurable during work and apparently increases with the work load. An increase of exercise pulmonary wedge pressure of a similar magnitude was observed after oral oxprenolol by Taylor *et al.* (1970). In this series, however, the effect of oxprenolol on pulmonary artery pressures and resistances and on pulmonary wedge pressure was less pronounced than that of propranolol. This supports the concept that oxprenolol does possess direct cardiostimulating properties besides its beta-receptor blocking action. The finding of an increased left ventricular filling pressure during long-term oral oxprenolol treatment during exercise but not at rest in the present study is consistent with this concept since the direct cardiostimulating action is known to be most effective at rest.

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# Diagnostic criteria for computer-aided electrocardiographic 15-lead system

## *Evaluation using 12 leads and Frank orthogonal leads with vector display*

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*The criteria for the diagnosis of myocardial infarction and ischaemic heart disease by an automated 15-lead computer-aided electrocardiographic system were examined using electrocardiograms of 543 patients. Errors in the electrocardiographic diagnosis were evaluated for each lead system (Frank orthogonal 3-lead, 12-lead, and hybrid 15-lead) using clinical and catheterization data for definitive diagnosis before review of the electrocardiograms and their reports. The effects of combinations of these diagnoses and additional ventricular conduction defects were also studied.*

*Myocardial infarction and left ventricular hypertrophy were more reliably diagnosed using 3-lead and 12-lead systems together than with either system alone. The most sensitive criteria for anterior infarction were a Q/R ratio in Z* $< 0{\cdot}1$ *and loss of the first 20 ms of anterior forces in the horizontal and sagittal planes of the vectorcardiogram. However, false positive results were frequent, particularly in association with left ventricular hypertrophy, non-specific intraventricular conduction defects, and left bundle-branch system block. Our V lead criteria were more specific whether or not these associated conditions were present. No single criterion with an acceptable false positive rate could be found to be sensitive for inferior infarction in all situations. Our most sensitive criteria were those based on the limb leads, and the presence of superior forces for the first 30 ms in the frontal plane of the vectorcardiogram, but these were better in combination. Limb lead criteria were the most specific. False positive results for inferior infarction were more frequent in the presence of left ventricular hypertrophy or ventricular conduction defects other than left anterior hemiblock.*

*ST and T wave abnormalities were more apparent in the 12 leads than in the orthogonal leads. Specificity and sensitivity of criteria were poor, and specificity was decreased and sensitivity was not significantly improved by combining 3-lead with 12-lead criteria. Because of frequent measurement errors of ST, T, and also Q waves by the computer programme, in practice we have achieved increased sensitivity in the diagnosis of ischaemia and infarction with the combination of 3-lead and 12-lead systems.*

*It is concluded that errors of diagnosis by a computer-aided system can be reduced by using multiple leads and that both 12-lead and orthogonal 3-lead systems are necessary for optimal computer diagnosis of left ventricular hypertrophy, myocardial infarction, and ischaemia.*

There is still controversy over the relative merits of 3-lead and 12-lead systems for computer electrocardiographic diagnosis (Caceres and Hochberg, 1970; Smith and Hyde, 1969; Bonner *et al.*, 1972; Cornfield *et al.*, 1973; Pordy *et al.*, 1968). The orthogonal 3-lead system is the simplest to use for such analysis, but the 12 praecordial and limb leads are more familiar to physicians. Comparisons of waveform measurements have suggested that the orthogonal system provides nearly all the information obtained from the 12-lead system in normal people (MacFarlane, Lorimer, and Lawrie, 1971; Pipberger *et al.*, 1961; Borun, Chapman, and

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Massey, 1966). Though some authors have found that the diagnostic accuracy of abnormalities of waveform is similar using the two systems (MacFarlane *et al.*, 1971; Pipberger *et al.*, 1961) others disagree (Bonner *et al.*, 1972; Borun *et al.*, 1966; Talbot *et al.*, 1973), and in most studies 3-lead and 12-lead systems have been compared only in relation to specific diagnoses (Eddleman and Pipberger, 1971).

Talbot *et al.* (1973) reported their experience using both 3-lead and 12-lead systems. They found that a 15-lead electrocardiographic system and logic derived from all these leads gave the best results for myocardial infarction and right bundle-branch system block, and increased sensitivity for most diagnoses. In view of observer variation in electrocardiographic reporting (Davies, 1958), an objective method to confirm computer diagnoses is preferable (Yano and Pipberger, 1964). Using objective confirmation, Eddleman and Pipberger (1971) concluded that the Frank orthogonal 3-lead electrocardiogram was more sensitive and as accurate as the 12-lead electrocardiogram using Minnesota code classification (Blackburn *et al.*, 1960) for the diagnosis of myocardial infarction. This code was designed for epidemiological studies and similar results may not be found with more sensitive 12-lead criteria.

We have, therefore, made a further comparison of orthogonal 3-lead, vectorcardiographic, and 12-lead criteria, used in our 15-lead computer programme (Talbot *et al.*, 1973). Necropsy and catheterization data provide the most accurate confirmation of electrocardiographic diagnoses. However, restriction of any study to diseases diagnosed by such methods will select those patients with more severe disease. We have used clinical information, supported by catheter data and a few necropsies, from men and women aged 40 to 80 years.

Multiple electrocardiographic abnormalities are frequent in clinical practice, and combinations of several abnormalities may have significance different from that of single ones. In this paper we have presented our results for patients with one or more myocardial infarcts, or myocardial ischaemia, alone or in combination. We have also examined the validity of these electrocardiographic criteria of infarction and ischaemia in the presence of left ventricular hypertrophy and ventricular conduction defects.

## Subjects and methods

Electrocardiograms were obtained using an on-line automated electrocardiographic system, which has been previously described (Scheinok *et al.*, 1972; Talbot *et al.*, 1973). Leads I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, and V6, and Frank XYZ leads were recorded simultaneously in groups of three leads. The three vector loops and the initial forces were obtained by digital-to-analogue conversion, displayed on an oscilloscope screen, and photographed with a high resolution camera. Electrocardiographic criteria were based on the 12 leads, the Frank XYZ leads, and the Frank vectorcardiogram, and hybrid criteria were formulated by combination of criteria from the three systems. However, not all statements were finally issued as an electrocardiographic report for clinical use. Some were suppressed by the computer but were preserved on a computer print-out. This enabled many different criteria and combinations of criteria to be assessed. Eighty-five per cent of all electrocardiograms recorded at Hahnemann Hospital are processed by computer.

Initially the scalar and vector electrocardiograms were examined to see whether the criteria in the programme for the diagnosis of myocardial infarction, left ventricular hypertrophy, or ischaemia, had been met. Frank 3-lead and 12-lead criteria were those in common use (Sokolow and Lyon, 1949; Allenstein and Mori, 1960; Sotobata, Richman, and Simonson, 1970; Chou and Helm, 1967; McConahay *et al.*, 1970; Gunnar *et al.*, 1967) and are presented in Table 1 which also includes vectorcardiographic criteria used in the hybrid programme.

We have already described our results in the diagnosis of conduction defects (Talbot *et al.*, 1973). In this study the following definitions have been used.

1) *Left bundle-branch system block:* QRS duration $\geqslant$115 ms and intrinsicoid deflection in lead X$\geqslant$60 ms; terminal R waves without Q waves in leads I or aVL.
2) *Complete right bundle-branch system block:* QRS duration $\geqslant$115 ms; terminal R′ wave in lead V1, and $R' \geqslant R+0{\cdot}2$ mV.

   Measurement of QRS duration was made in orthogonal leads, with limits based on the 95th centile of our normal population (Talbot *et al.*, 1974). In fact, complete bundle-branch system blocks almost invariably showed a QRS duration $\geqslant$99th centile, i.e. 125 ms.
3) *Left anterior hemiblock:* QRS axis between –45° and –90° if there were a Q wave in aVL (Rosenbaum, 1969). Usually this diagnosis was associated with a QRS duration >90 ms (i.e. the lower limit of the 95th centile plus 20 ms). The diagnosis of left anterior hemiblock was not made if the R voltage in all limb leads was less than 0·5 mV.

TABLE 1

| *Diagnosis* | *12-lead criteria (A)* | *Orthogonal/lead criteria (B)* | *Vectorcardiographic criteria (C)* | *References* |
|---|---|---|---|---|
| Anterior infarction | R waves $<0{\cdot}1$ mV or QR with Q $\geqslant 0{\cdot}3$ mV in 2 leads of V2–V4 | Q/R ratio in Z $<0{\cdot}1$ | Loss of first 20 ms anterior forces in XZ and YZ planes | (B) Eddleman and Pipberger (1971)<br>(C) Chou and Helm (1967) |
| Inferior infarction | Q waves $\geqslant 0{\cdot}2$ mV and 30 ms in 2 leads of II, III, and aVF | Q/R ratio in Y $\geqslant 0\ 25$ | Superior forces for first 30 ms (–20 to –180° in XY plane) | (B) Eddleman and Pipberger (1971)<br>(C) Chou and Helm (1967) |
| Lateral infarction | QR waves in V5 and V6 (Q $\geqslant 0\ 3$ mV) or R $\leqslant 0{\cdot}1$ mV in these leads | Q/R ratio in X $\geqslant 0{\cdot}20$ | | (B) Modified from Eddleman and Pipberger (1971) |
| Left ventricular hypertrophy | R V5 or V6 + SV1 $\geqslant 3{\cdot}7$ mV or R $\geqslant 2{\cdot}7$ mV in V5 or V6 or R $\geqslant 1{\cdot}6$ mV in aVL | Voltage of R or S wave $>2{\cdot}2$ mV in X, Y or Z | Maximum spatial QRS voltage $>2{\cdot}0$ mV | (A) Sokolow and Lyon (1949)<br>(B) and (C) Chou and Helm (1967); Yano and Pipberger (1964) |
| Anterior ischaemia | T inversion in V1 to V3, or V3 and V4 (T equal to or more negative than $-0{\cdot}1$ mV) | T inversion in X (T equal to or more negative than $-0{\cdot}1$ mV) or T upright and equal to or more than 0 2 mV in Z | | |
| Anterolateral ischaemia | T inversion in V5 and V6 (T equal to or more negative than $-0{\cdot}1$ mV) or T wave inversion of more than 0·2 mV in either V5 or V6 | T inversion equal to or more than 0·2 mV in X | | |
| Inferior ischaemia | T inversion of more than 0·1 mV in 2 leads of II, III, or aVF | T inversion equal to or more than 0·2 mV in Y | | |
| ST displacement (+ or –ve) | Difference of $\geqslant 0{\cdot}15$ mV in ST compared with baseline | Difference of $\geqslant 0{\cdot}15$ mV in ST compared with baseline | | |

4) *Intraventricular conduction delay:* QRS duration $\geqslant 115$ ms, with no other criteria for bundle-branch system block.

Combined (hybrid) criteria for inferior and anterior infarction are described in Appendix A. If criteria from the 3 orthogonal leads or the vectorcardiogram or the 12 leads were fulfilled, this was described as 'or-logic'; and if criteria from either the 3 orthogonal leads or the vectorcardiogram, together with criteria from the 12 leads, were fulfilled, this was described as 'and-logic' (Talbot *et al.,* 1973). Therefore, 'and-logic' required criteria from two or more of the three systems to be fulfilled. Diagnoses were assigned qualitative probability but for this study the definite, 'probable', and 'possible' reports have been amalgamated.

All electrocardiograms recorded during a seven-week period were selected for inclusion in this study, if reported by the computer (using either 3-lead, 12-lead, or hybrid criteria) to show inferior or anterior infarction, left ventricular hypertrophy, left or right bundle-branch system block, left anterior hemiblock, a non-specific intraventricular conduction defect, or any combination of these. Some electrocardiograms selected had been included in a previous study (Talbot *et al.,* 1973). Electrocardiograms were examined only after a complete medical record had been obtained and the clinical diagnosis determined by criteria outlined in Appendix B. In this study 961 electrocardiograms (165 men and 94 women) were examined. The diagnosis was confirmed at necropsy in 4 patients, coronary arteriography in 25, and cardiac catheterization and operation in 19. Such a study cannot include all electrocardiograms with false negative diagnoses.

To avoid this bias in favour of computer criteria, we examined the final diagnosis for each patient in hospital during this period; if the diagnosis were myocardial infarction or if a cause for left ventricular hypertrophy could be established (see Appendix B) the electrocardiograms were examined. This group comprised 908 electrocardiograms from 112 men and 70 women. For analysis of myocardial ischaemia, we examined an additional 289 electrocardiograms from 102 patients coded as ischaemic heart disease (400–404 and 410, International Classification of Diseases, 8th Revision, 1967–1969) and confirmed by coronary angiography.

Each electrocardiogram was examined for diagnostic features of myocardial infarction, left ventricular hypertrophy, and ischaemia (Table 1). These features included all the criteria, including the hybrid criteria described. From this analysis computer measurement errors were identified and all other errors of diagnosis in relation to the clinical diagnosis were described as criteria errors. In all, 1869 electrocardiograms of 441 patients were examined for accuracy of diagnostic statements of myocardial infarction and left ventricular hypertrophy and 2158 electrocardiograms (543 patients) were examined for ST and T wave abnormalities. The latter were divided into ST segment depression and ST segment elevation, specific T wave abnormalities of ischaemia as detailed in Table 1, and non-specific T wave abnormalities, consisting of all T wave abnormalities in any one of the 12 leads, and T waves of 0·1 mV or less in multiple leads, or X, Y, or Z, which could not be described as diagnostic of ischaemia.

The majority of errors of diagnosis were criteria errors. Separate analysis of the results from the three groups of electrocardiograms did not lead to any different conclusions, and the results have therefore been amalgamated. Only the 12-lead, orthogonal 3-lead, and vectorcardiographic criteria that were found most satisfactory have been presented.

In this study we have clearly distinguished between false positive criteria and false positive measurement errors, but have not detailed false negative results because of our inability to localize the areas of ischaemia or infarction by coronary arteriography.

## Results

The results of anterior and inferior infarction criteria are shown in Table 2. Myocardial infarction

TABLE 2 *Comparison of diagnostic criteria* for myocardial infarction*

| *Clinical group* | *Electrocardiographic lead system* | *Anterior infarction criteria positive* | | | *Inferior infarction criteria positive* | | | *No ECG criteria of infarction* | *Total ECGs on patients with infarction* |
|---|---|---|---|---|---|---|---|---|---|
| | | *Clinical criteria for infarction present* | *No clinical infarction* | *False positive (%)* | *Clinical criteria for infarction present* | *No clinical infarction* | *False positive (%)* | | |
| I Myocardial infarction only | a) 12-lead | 101 | 18 | (15·1) | 135 | 22 | (14) | 153 | 343 |
| | b) XYZ leads | 181 | 38 | (17·4) | 89 | 8 | (8·3) | 136 | 343 |
| | c) Vector | 167 | 24 | (12·6) | 134 | 29 | (17·7) | 108 | 343 |
| | d) Hybrid 15-lead | 190 | 45 | (19·1) | 136 | 14 | (9·3) | 97 | 343 |
| II Myocardial infarction and left ventricular hypertrophy | a) 12-lead | 105 | 28 | (21·1) | 127 | 27 | (17·5) | 65 | 280 |
| | b) XYZ leads | 162 | 84 | (34·1) | 79 | 20 | (20·2) | 81 | 280 |
| | c) Vector | 159 | 81 | (33·8) | 137 | 64 | (37·4) | 42 | 280 |
| | d) Hybrid 15-lead | 184 | 99 | (35·0) | 128 | 29 | (18·5) | 31 | 280 |
| III Myocardial infarction and intraventricular conduction defect | a) 12-lead | 18 | 7 | (28·0) | 44 | 10 | (18·5) | 39 | 97 |
| | b) XYZ leads | 12 | 13 | (52·0) | 29 | 2 | (6·4) | 65 | 97 |
| | c) Vector | 11 | 11 | (50·0) | 42 | 9 | (17·6) | 53 | 97 |
| | d) Hybrid 15-lead | 16 | 22 | (57·9) | 47 | 10 | (17·5) | 45 | 97 |
| IV Myocardial infarction and RBBB | a) 12-lead | 31 | 9 | (22·5) | 58 | 24 | (29·3) | 30 | 105 |
| | b) XYZ leads† | — | — | — | 42 | 8 | (16·0) | — | 105 |
| | c) Vector | 36 | 13 | (26·5) | 48 | 17 | (26·1) | 33 | 105 |
| | d) Hybrid 15-lead | 42 | 13 | (23·6) | 57 | 25 | (30·4) | 21 | 105 |
| V Myocardial infarction and LAHB | a) 12-lead | 44 | 4 | (8·3) | 46 | 2 | (4·1) | 22 | 108 |
| | b) XYZ leads | 68 | 5 | (6·8) | 45 | 0 | (0) | 14 | 108 |
| | c) Vector | 66 | 5 | (7·0) | 45 | 0 | (0) | 22 | 108 |
| | d) Hybrid 15-lead | 81 | 7 | (8·0) | 51 | 2 | (3·8) | 6 | 108 |

*Excluding measurement errors.

Percentages of false positive diagnoses were calculated in relation to electrocardiographic diagnoses and are shown in parentheses. Details of criteria are in Table 1 and Appendix A.

†Orthogonal criteria for anterior infarction and right bundle-branch block are not presented because of the low R wave voltage of Z and therefore inaccurate values of Q/R ratio in Z.

*Abbreviations:* RBBB=right bundle-branch block; LAHB=left anterior hemiblock.

is often present even when electrocardiographic features are not. We have, therefore, concluded that the criterion most often found in association with clinical evidence of infarction was the most sensitive sign of infarction in this area. Criteria were often fulfilled for different localizations of infarction in the same patient using different systems; for this reason separate analysis of anterior and inferior criteria together, anterior criteria alone, and inferior criteria alone would be misleading.

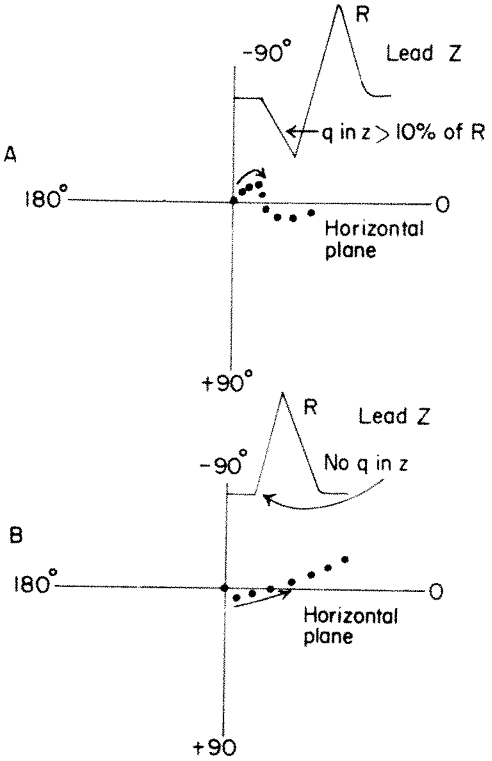

FIG. 1 *Diagrammatic representation of the initial 40 ms forces of the horizontal plane of the vectorcardiogram and lead Z of the Frank electrocardiogram. (A) The initial 20 ms forces of the vectorcardiogram are directed posteriorly and yet Q/R ratio is normal. No initial R wave was detected by the computer or the cardiologist though a small R wave must have been present simultaneously with the initial 20 ms forces of the vectorcardiogram. (B) The initial 10 ms forces of the vectorcardiogram are slightly anterior but the later forces are posterior. No Q wave in lead Z was detected by the computer or the cardiologist though a small Q wave must have been present simultaneously with the initial 10 ms forces of the vectorcardiogram.*

## Anterior myocardial infarction

The most sensitive criterion for anterior infarction was a Q/R ratio in Z $< 0{\cdot}1$, but loss of anterior forces in the sagittal and horizontal planes of the vectorcardiogram was almost as sensitive. Computer hybrid criteria were even more sensitive, because of occasional discrepancies between these two diagnostic criteria. In some infarctions (Fig. 1A) there was early posterior orientation of initial forces for 20 ms (XZ plane), which then turned sharply forward so that the Q/R ratio in Z was preserved, whereas in others the first 10 ms forces were anterior though the next 20 ms forces were posterior (Fig. 1B). Early posterior orientation of horizontal forces was often associated with a narrow R wave in V1 to V3. Occasionally the only positive indication of old anterior infarction was a Q wave of 0·1 mV and less than 20 ms duration in two of the three leads V2, V3, and V4, but an isolated small Q wave in the transition zone was not significant. Associated left ventricular hypertrophy produced more false-positive results, particularly with orthogonal and vectorcardiographic criteria, but there were few electrocardiograms of patients with infarction in which the diagnosis was not suggested by 15 leads (Fig. 2).

Left bundle-branch system block was found in only 20 electrocardiograms of patients with infarction; though a hybrid 15-lead diagnosis of anterior infarction was correctly made in 17 electrocardiograms, there were 48 (73·8%) false-positive results, mainly because of vectorcardiographic and orthogonal criteria. Q waves rarely spread to V4 in the absence of infarction. Right bundle-branch system block was not associated with significantly more false-positive results, but Q waves in V1 to V3 were sometimes falsely detected, probably because of the low voltage of the initial R wave. The R wave in lead Z is often of low voltage in right bundle-branch system block, so that in our experience the Q/R ratio in Z is not satisfactory in this condition. However, the absence of a Q in Z is an indication of anterior myocardial infarction. Right bundle-branch system block was particularly associated with QR complexes in V1 to V4, but QR complexes were of more significance than QS waves in all conditions except in V4. Left anterior hemiblock did not appear to affect the diagnosis of anterior infarction. Non-specific intraventricular conduction defects reduced the specificity of all criteria for anterior infarction and sensitivity may also have been reduced.

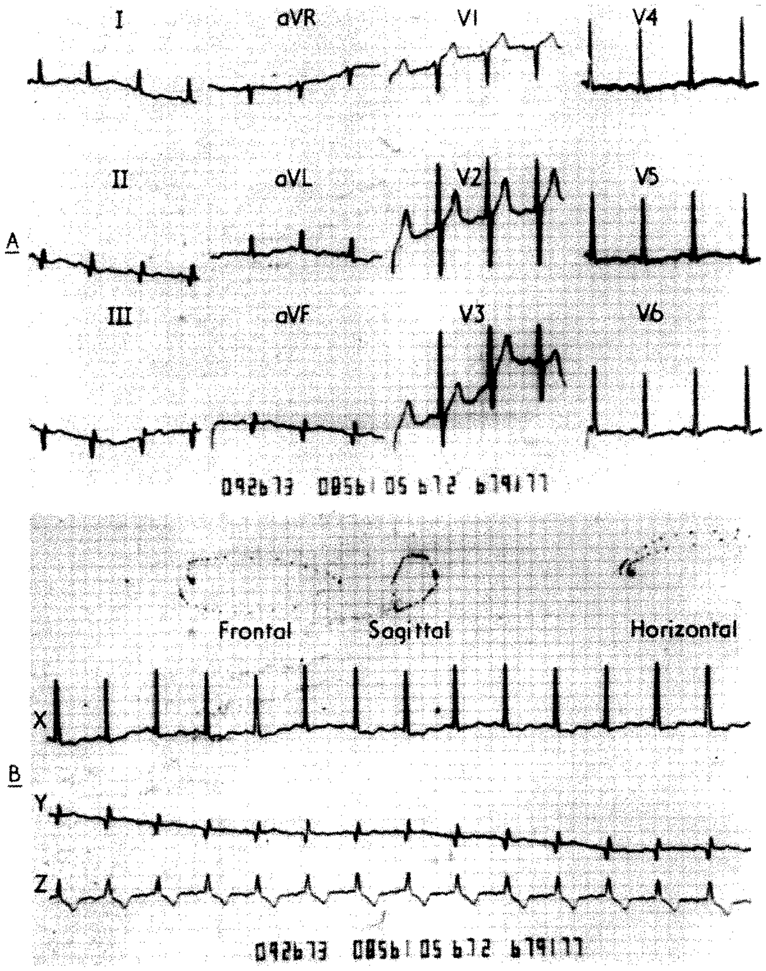

FIG. 2 *Electrocardiograms and vectorcardiographic loops of a 52-year-old man. Serial records had shown the development of inferior and true posterior infarction, with a prominent R wave in V1 and V2. There was clinical evidence of myocardial infarction initially and further infarction developed six months later. (A) The 12-lead electrocardiogram at this time is shown. This did not show any significant change from the earlier record. (B) Vectorcardiogram and orthogonal leads. Above, from left to right: frontal, sagittal, and horizontal plane vector loops. Below, orthogonal leads X, Y, and Z. Both the Q wave in Z and anterior forces were lost, compared with the electrocardiogram taken six months earlier. The rightward orientation of the initial forces probably indicates lateral infarction as well. These changes persisted, and show the value of Frank 3 leads for the sensitive diagnosis of anterior myocardial infarction.*

## Inferior myocardial infarction

The most sensitive of the selected single-lead criteria for inferior infarction was the presence of a Q wave in lead aVF of $\geqslant$0·2 mV. In fact Q waves of 0·1 mV were even more sensitive and Q waves of 0·1 mV in leads II, III, and aVF were usually associated with clinical infarction. Loss of inferior forces was also a sensitive criterion but, as with Q in lead III alone, produced an unacceptable number of false-positive results, particularly in the presence of left ventricular hypertrophy. False negative results occurred in typical inferior infarction when there was associated lateral infarction in which initial forces in the frontal plane were sometimes diverted to the right and slightly inferiorly,

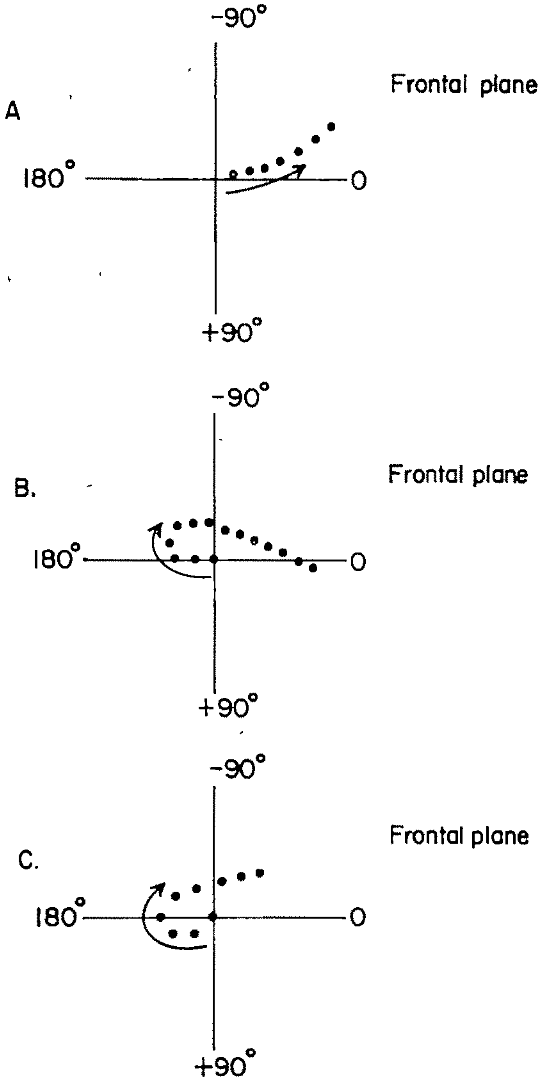

FIG. 3 *Frontal plane vectors in inferior infarction (5 ms interval markers). (A) The initial forces are directed superiorly and to the left at –20° with counterclockwise rotation. However, there is distinct left axis deviation. (B) The initial 10 ms forces are horizontal but the rotation of the loop is clockwise and the axis is horizontal. (C) The initial 10 ms forces are directed inferiorly and to the right before turning clockwise and to the left. The axis is usually horizontal. The first configuration may or may not be associated with inferior infarction; the latter two usually are associated with inferior infarction.*

but Q waves were present in leads II and aVF (or Y) (Fig. 3).

Left ventricular hypertrophy was associated with superior forces for the initial 30 ms when the frontal plan QRS axis was vertical ($\geqslant +45°$) in the absence of infarction; this increased the number of false-positive results for inferior infarction in all lead systems. In the presence of left bundle-branch system block and left anterior hemiblock (or left axis deviation), R waves were often small in the absence of infarction and Q waves occasionally appeared in III and aVF but not in II. False-positive results were common in the presence of combined right bundle-branch system block and left anterior hemiblock, probably because a very small initial R wave was not detected; this was followed by a conspicuous S wave before the terminal R′ wave in III and aVF. The vectorcardiogram was often necessary to confirm initial inferior forces. Non-specific intraventricular conduction defects were commonly found in association with criteria of inferior infarction and slightly increased false-positive results.

### Optimal computer criteria for infarction

Hybrid computer criteria were the most sensitive for anterior and inferior infarction, and the presence of specific criteria resulting in a diagnosis of probable or definite infarction correlated well with the clinical diagnosis. The most specific criteria for inferior and anterior infarction have been tested (Table 3) so that diagnoses can be assigned a degree of probability. Loss of specificity for anterior infarction resulted from inclusion of the Q wave in V3 without Q in V4, particularly in association with left ventricular hypertrophy and intraventricular conduction defects, and there was loss of specificity for inferior infarction with reduction of Q/R ratios. We noted that Q/R ratios were valid even with Q waves of 0·1 mV, when a W-shaped complex was often seen. The Q wave in III added little that could not be obtained from aVF alone, and a Q wave $\geqslant 0{\cdot}2$ mV in lead aVF was only slightly more specific and less sensitive than the 12-lead combined criteria of the computer programme. However, the additional presence of a Q wave of $\geqslant 0{\cdot}2$ mV in II, particularly if the Q/R ratio $\geqslant 25$ per cent, considerably enhanced the specificity of a Q wave in III or aVF. Even a Q wave of 0·1 mV in II was supportive evidence for other criteria of inferior infarction. A Q/R ratio in II, III, and aVF of over 0·25 was almost diagnostic of inferior infarction, and was associated with a rightward and superior direction of the initial 30 ms forces in the frontal plane.

TABLE 3 *Specific diagnostic criteria**

| | *Positive criteria for inferior infarction*** | | | | *Positive criteria for anterior infarction*** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Q/R in II+III+aVF ≥0·25* | *Q/R in II+aVF ≥0·25* | *Q Waves in II+III+aVF ≥0·2 mv* | *Q Waves in II+aVF ≥0·2 mv* | *Q Waves in V2–V4* | *Q Waves in V3+V4* | *Q Waves in V4* | *Q Waves in V2+V3* | *Q Waves in V3* |
| Clinical criteria for infarction present | 181 | 186 | 299 | 314 | 146 | 213 | 223 | 277 | 315 |
| False positive† | 15 (7·7) | 17 (8·4) | 30 (9·1) | 39 (11·0) | 12 (7·6) | 20 (8·6) | 22 (9·0) | 63 (18·5) | 68 (17·8) |

*Excluding patients with left bundle-branch block. Total number of electrocardiograms examined=933.
**Less specific criteria are not shown. Specificity increases from right to left for both inferior and anterior infarction criteria.
†Percentage of false positives in parentheses.

## Lateral infarction

Criteria for lateral infarction were only fulfilled in 15·2 per cent of cases with myocardial infarction. Though the presence of Q waves in leads V5 and V6 together did decrease sensitivity, this combination was still superior to the Q/R ratio ≥0·20 in X. No example of high lateral infarction with changes confined to leads I and aVL or high praecordial leads was noted during this study. During the period of the study, 11 electrocardiograms (2 patients) were found in which criteria for lateral infarction only were satisfied; in these electrocardiograms the V-lead criteria were superior to Q/R ratio in lead X.

## Myocardial ischaemia

ST and T wave criteria errors in 3-lead and 12-lead electrocardiograms are shown in Table 4. A separate analysis of T wave abnormalities for each

TABLE 4 *Diagnostic accuracy of ST and T wave criteria for ischaemia*

| *Electrocardiographic diagnosis* | *Clinical diagnosis* | *No other abnormality* | | *Left ventricular hypertrophy* | |
|---|---|---|---|---|---|
| | | *XYZ* | *12-lead* | *XYZ* | *12-lead* |
| **Anterolateral ischaemia* | | | | | |
| T inversion V5 and V6 | Clinical and electro-cardiographic positive | 184 | 209 | 84 | 99 |
| T inversion in X | False positive criteria† | 9 (4·7) | 10 (4·6) | 259 (75·5) | 269 (73·1) |
| **Anterior ischaemia* | | | | | |
| T inversion in any 2 leads of V2 to V4 | Clinical and electro-cardiographic positive | 12 | 24 | 8 | 19 |
| T upright in Z, T inversion in X | False positive criteria† | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Inferior ischaemia* | | | | | |
| T inversion in any 2 leads of II, III, aVF | Clinical and electro-cardiographic positive | 70 | 92 | 30 | 42 |
| T inversion in Y | False positive criteria† | 0 (0) | 0 (0) | 41 (57·7) | 44 (51·2) |
| *Inferior ST depression* | | | | | |
| ST depression in any 2 leads of II, III, aVF | Clinical and electro-cardiographic positive | 7 | 13 | 8 | 16 |
| ST depression in Y | False positive criteria† | 0 (0) | 0 (0) | 11 (57·9) | 22 (57·9) |
| *Anterior ST depression* | | | | | |
| ST depression in any 2 leads of V2 to V6 | Clinical and electro-cardiographic positive | 71 | 86 | 67 | 76 |
| ST depression in X | False positive criteria† | 3 (4·1) | 6 (6·5) | 149 (69·0) | 168 (68·9) |
| *ST elevation* | | | | | |
| ST elevation in any 2 leads of V1 to V6 | Clinical and electro-cardiographic positive | 47 | 59 | 6 | 9 |
| ST elevation in X | False positive criteria† | 1 (2·1) | 0 (0) | 2 (25) | 2 (18·4) |
| *Non-specific T wave changes* | | 234 | 240 | 179 | 152 |
| *Normal T waves* | | 119 | 79 | 25 | 18 |
| *Total number of electrocardiograms with ischaemia* | | 589 | | 316 | |

*Some patients showed both inferior and anterior ST and T wave changes, see Table 1 and text for full criteria
†Percentages of false-positive results are in parentheses.

conduction defect was performed, and since T wave abnormalities in the presence of left bundle-branch system block did not appear to be of diagnostic value, they have been excluded from this table. ST depression and T wave changes were not specific for ischaemia even if there were normal intraventricular conduction and no evidence of left ventricular hypertrophy. Specificity of T wave inversion and ST depression in both 3-lead and 12-lead electrocardiograms was reduced in the presence of left ventricular hypertrophy, particularly if there were electrocardiographic features of left ventricular hypertrophy. Sensitivity was greater for the 12-lead than for 3-lead criteria, and this was out of proportion to the slightly greater diagnostic specificity of our 3-lead criteria for anterior ischaemia. The 3-lead criteria of this programme were particularly insensitive to anterior without lateral ischaemic changes, and better 3-lead criteria must be devised. False-positive results for anterior ischaemia occur in the presence of right bundle-branch system block, since T wave inversion, sometimes with ST depression, can extend as far as V3 in the absence of ischaemia, and this statement is suppressed by the computer. ST segment depression, particularly in inferior leads, was moderately specific for ischaemia in the absence of left ventricular hypertrophy, non-specific intraventricular conduction defects, or right bundle-branch block. It was noted that T wave inversion without ST segment depression was of greater diagnostic value for ischaemia than similar T wave inversion with ST segment depression in the presence of left ventricular hypertrophy, non-specific intraventricular conduction defects, or right bundle-branch block. Inferior ST and T wave changes were more specific than those in V5 and V6, but they were less frequent. There were rarely normal T waves in the presence of ischaemic heart disease and left ventricular hypertrophy. ST elevation was specific for ischaemia in all conditions.

| *Left ventricular hypertrophy and any ventricular conduction defect* | | *Any ventricular conduction defect alone* | |
|---|---|---|---|
| *XYZ* | *12-lead* | *XYZ* | *12-lead* |
| 18 | 24 | 29 | 32 |
| 52 (74·3) | 67 (73·6) | 65 (69·1) | 76 (70·9) |
| 13 | 18 | 13 | 25 |
| 4 (23·5) | 12 (40·0) | 5 (27·8) | 18 (41·8) |
| 9 | 11 | 18 | 24 |
| 9 (50·0) | 10 (47·6) | 3 (14·3) | 4 (14·3) |
| 4 | 5 | 2 | 2 |
| 2 (33·3) | 2 (28·6) | 15 (8·8) | 16 (8·9) |
| 48 | 52 | 47 | 57 |
| 75 (61·0) | 90 (63·4) | 78 (62·4) | 87 (60·4) |
| 4 | 5 | 1 | 1 |
| 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 87 | 80 | 100 | 83 |
| 1 | 0 | 20 | 16 |
| 123 | | 176 | |

## Measurement errors

Errors of measurement of QRS, which resulted in false positive diagnoses of myocardial infarction occurred sometimes in the 12-lead system and sometimes in the orthogonal lead system and vectorcardiogram. An irregular baseline, as with atrial fibrillation or flutter or technical difficulties, was an important cause of error particularly affecting measurement of the Q wave. Because of discrepancies between these systems the 15-lead system led to improvement in sensitivity of diagnosis.

Measurement errors of the ST segment and T wave in a sub-sample of 786 electrocardiograms compared with the cardiologist's interpretation are shown in Table 5. Orthogonal leads were not only less sensitive to ST and T wave changes, but there were as many errors of measurement in this system as in the V leads. The computer programme failed to detect ST changes in both 12 leads and orthogonal leads and there were both false-positive and false-negative results for T wave changes. Occasionally ST elevation or depression was incorrectly reported. The principal discrepancy between orthogonal and 12-lead systems was T wave inversion in V1 to V4 (anterior ischaemia); this abnormality was often not visible in orthogonal leads. Occasionally this V-lead diagnosis was made incorrectly in the presence of a negative QRS and a pronounced upwards ST slope merging into the T wave, when the latter part of the positive T wave was considered to be inverted in these leads by the computer.

## Discussion

Most studies of orthogonal, vectorcardiographic, and 12-lead criteria have been concerned with the

TABLE 5 *Accuracy of computer diagnosis of ST and T wave changes (measurement errors)**

| *Electrocardiographic diagnosis* | *XYZ leads* | | | | *12 leads* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Total number of cardiologist's statements* | *Computer and cardiologist positive* | *False positive computer diagnosis*† | *False negative computer diagnosis* | *Total number of cardiologist's statements* | *Computer and cardiologist positive* | *False positive computer diagnosis*† | *False negative computer diagnosis* |
| Anterolateral ischaemia | 225 | 198 | 3 (1·5) | 27 | 255 | 222 | 4 (1·8) | 33 |
| Inferior ischaemia | 77 | 64 | 3 (4·5) | 13 | 103 | 79 | 2 (2·5) | 24 |
| Anterior ischaemia | 22 | 21 | 0 (0) | 1 | 40 | 34 | 1 (2·9) | 16 |
| Anterior or inferior ST elevation | 50 | 20 | 0 (0) | 30 | 61 | 22 | 2 (8·3) | 39 |
| Anterior ST depression | 164 | 129 | 8 (5·8) | 35 | 213 | 168 | 11 (6·1) | 35 |
| Inferior ST depression | 10 | 9 | 1 (10) | 1 | 22 | 18 | 1 (5·3) | 4 |
| Non-specific T changes | 326 | 235 | 2 (0·8) | 91 | 315 | 231 | 2 (0·4) | 84 |

*The computer statement has been compared with the cardiologist's interpretation using the same criteria as produced the computer statement.

†Percentage false positive statements, in parentheses, are expressed in relation to the number of positive electrocardiographic diagnoses by computer.

diagnostic accuracy of such criteria, using various mathematical methods (Simonson, 1961), which assign equal importance to false-positive and false-negative results. However, in epidemiological and clinical work, requirements may differ, and statements of both specificity and sensitivity may be necessary.

The sensitivity of any test is measured by the percentage of people with the disease under consideration, who are correctly classified by the test. Specificity is calculated from the percentage of people without the disease, who have a negative result to the test. Sensitivity is affected by the population examined. Mildly affected patients may not be subjected to the test, and test records of more severe cases may not be obtainable for logistic or humanitarian reasons. Also, specificity (by the definition given) is greatly affected by the variety of clinical conditions in the population which are frequently confused with the diagnosis under investigation. A more useful measurement is the predictability of the test, i.e. the percentage of correct positive diagnoses by the test in relation to the total number of positive tests. The predictability of the electrocardiographic criteria and the percentage of false-positive results have been measured in this study, but this is only related to specificity in the hospital population examined and might not be applicable in other situations.

Myocardial infarction cannot be localized without pathological or electrocardiographic information, and therefore false-positive results may actually be higher than indicated. We cannot determine the frequency of false-negative electrocardiographic diagnoses without necropsy evidence. For all these reasons the proportion of false-negative diagnoses and sensitivity cannot be determined. However, if there has been no selection of cases, the diagnostic sensitivity of different criteria in various conditions can be and has been compared. Catheterization data have been used for infarct localization (McConahay *et al.*, 1970), but with diffuse arteriographic disease, localization of infarction is only presumptive. Various clinical methods have been used to circumvent this difficulty, e.g. use of generally accepted 12-lead criteria (Eddleman and Pipberger, 1971) or the time sequence of evolutionary changes in relation to the history and investigations (Young and Williams, 1968; Goldberger, 1945). We have analysed our results by these methods, but they are open to criticism and the results did not affect our conclusions.

The electrocardiogram may be normal in the presence of infarction, and may vary from day to day; therefore no criterion can be absolutely specific or sensitive (Cawood *et al.*, 1974a, b; Willems, Poblete, and Pipberger, 1972). The results of this study suggest that diagnostic sensitivity for myocardial infarction and ventricular conduction defects is usually improved by 15-lead hybrid criteria and that the computer statement of probable or definite infarction corresponds satisfactorily with the actual diagnosis.

Superior forces for ⩾30 ms and clockwise inscription of the first 25 to 30 ms in the frontal plane have been proposed as sensitive criteria for inferior infarction (McConahay *et al.*, 1970; Young and Williams, 1968; Hugenholtz, Forkner, and Levine, 1961; Murata *et al.*, 1967). It has been suggested that the vectorcardiographic appearance of inferior infarction is preserved in the presence of left anterior hemiblock (Kulbertus *et al.*, 1971). However, this study suggests that vectorcardiographic criteria are no more sensitive than 12-lead criteria. Vector loops may vary considerably and the initial inscription is affected by the later direction of the QRS; clockwise rotation may occur without infarction if there is a vertical axis ($\geqslant +45°$) and inferior infarction may occur with counterclockwise rotation, particularly with left-axis deviation (Gunnar *et al.*, 1967), and sometimes with left anterior hemiblock. A Q/R ratio $\geqslant 25$ per cent in aVF may be the best single discriminating factor between normal hospital patients and patients with inferior infarction (Simonson, 1961). Increasing duration of the Q wave increases specificity (Myers, Klein, and Hiratzka, 1949), and a Q wave duration $>0{\cdot}04$ s in aVF is the next most accurate single-lead criterion (Simonson, 1961). However, combinations of leads have not been tested adequately.

Specific vectorcardiographic appearances in the horizontal plane have been described for anterior infarction (Hugenholtz *et al.*, 1963), and it has been thought that these remain specific in the presence of left ventricular hypertrophy. Our results and those of others (Kini, Eddleman, and Pipberger, 1970) conflict with this view. All criteria of anterior infarction were less specific in the presence of left ventricular hypertrophy; the vectorcardiographic and orthogonal criteria were less specific than the V lead criteria, though QS waves in V1 and V2 and sometimes also in V3 were frequent findings in uncomplicated left ventricular hypertrophy.

The diagnosis of inferior or anterior infarction cannot be made by usual criteria in the presence of left bundle-branch system block because of frequent false-positive results. Moreover, left bundle-branch system block may conceal the changes of anterior and inferior infarction (Luy, Bahl, and Massie, 1973). The diagnosis of left anterior hemiblock did not appear to influence the diagnosis of inferior or anterior infarction. Though it has been pointed out that the changes of inferior infarction and anteroseptal infarction may be modified by left anterior hemiblock as a result of inferior direction of the initial 20 ms forces, this does not seem of great importance. In our experience, right bundle-branch system block has little effect on the diagnosis of inferior and anterior infarction, in contrast with the findings of Goldman and Pipberger (1969). Occasionally there was an increase in the initial anterior 20 ms forces in patients with infarction who developed right bundle-branch system block, even if there were V-lead electrocardiographic evidence of anterior infarction on the previous tracing. This increase of anterior forces might occasionally obscure anterior infarction or suggest true posterior infarction, and should be suspected if there is clockwise rotation of the vector loop in the horizontal plane. In conclusion, criteria which are used for the diagnosis of inferior and anterior infarction have been arranged in order of increasing sensitivity and decreasing specificity in Table 6.

Many factors influence ST and T wave changes (Varriale, Alfenito, and Kennedy, 1966), and we, therefore, do not use them for left ventricular hypertrophy diagnostic logic. This study indicated that the diagnosis of left ventricular hypertrophy was not supported by the presence of intraventricular conduction defect or delayed intrinsicoid deflection as was suggested by Estes (1966), though

TABLE 6 *Diagnostic criteria for a computer system**

| *Inferior infarction†* | *Anterior infarction†* |
|---|---|
| 1) Q II, III, and aVF (or Y) $\geqslant 0{\cdot}2$ mV and $\geqslant 25\%$ of R wave | 1) Q V2, V3, and V4 |
| 2) Q II, III, and aVF (or Y) $\geqslant 0{\cdot}1$ mV and $\geqslant 25\%$ of R wave | 2) Q V3 and V4 |
| 3) Q II and aVF (or Y) $\geqslant 0{\cdot}2$ mV and $\geqslant 25\%$ of R wave | 3) QR V2 and V3 |
| 4) Q III, and aVF (or Y) $\geqslant 0{\cdot}2$ mV and $\geqslant 25\%$ of R wave and Q II $\geqslant 0{\cdot}2$ mV | 4) QR V4 |
| 5) Q II and aVF (or Y) $\geqslant 0{\cdot}2$ mV only and Q III $\geqslant 0{\cdot}2$ mV and $\geqslant 25\%$ of R wave | 5) QR V3 |
| 6) Q II, III, and aVF (or Y) $\geqslant 0{\cdot}2$ mV only | 6) QR V2 |
| 7) Q II $\geqslant 0{\cdot}2$ mV only, Q aVF (or Y) $\geqslant 0{\cdot}2$ mV and $\geqslant 25\%$ of R wave | 7) QS V2 and V3 |
| 8) Q II, III, and aVF (or Y) $\geqslant 0{\cdot}2$ mV only | 8) QS V3 |
| 9) Q III and aVF $\geqslant 0{\cdot}2$ mV only | 9) QS V2 |
| 10) Q aVF $\geqslant 0{\cdot}2$ mV only | 10) Q V2 or V3 |
| 11) Superior forces for $\geqslant 30$ ms in frontal plane of VCG | 11) Q V2 or V3 or V4 |
| | 12) First 20 ms forces posterior in horizontal and sagittal planes of VCG |
| | 13) Q in Z $<10\%$ of R wave |

*Criteria are arranged in order of increasing specificity and decreasing sensitivity from below upwards.

†Q waves all of $\geqslant 30$ ms for inferior infarction and Q waves all of $\geqslant 20$ ms in V leads for anterior infarction.

in patients under 37 years of age, in whom multiple disorders are uncommon, such criteria might be of value. The gradual slope of ST depression from a normal J point to a wholly inverted T wave or an initially inverted T wave, often with a terminal upright T wave in anterolateral leads, is more typical of left ventricular hypertrophy than of ischaemia, but such appearances are difficult to quantify and may be misleading. Repolarization changes particularly in the frontal plane may be the result of left anterior hemiblock (Gomes, Lima, and Romalhao, 1975). Descriptive statements about ST segment deviation and T wave inversion were issued by the computer and were clinically useful; only if there are pronounced ST segment changes can they be used to support a diagnosis of infarction.

Description of ST and T wave changes forms an important part of an electrocardiographic report. Because of the lack of sensitivity of our orthogonal lead criteria for ST and T wave changes and measurement errors, false-negative interpretation may occur. Though it is possible that better criteria could be devised, the criteria used had been found to produce the most acceptable number of false-positive and false-negative results. Further criteria based on the orthogonal leads and vectorcardiographic T wave loops may be of value when data from such loops have been quantified satisfactorily, but so far we have had little success with simple angular criteria. A 12-lead electrocardiogram may appear to reduce criteria errors to a satisfactory level, but the use of 15 leads with hybrid 'or-logic' reduces false-negative measurement errors and increases sensitivity of diagnosis; this increases false-positive results, and necessitates further hybrid 15-lead 'and-logic' so that more definite T wave statements can be made.

At present it is impossible to report quantitative levels of probability, since though the range of electrocardiographic measurements for the population is known, it is necessary to have these from cases with all the diagnoses causing false-positive and false-negative computer reports. It is often difficult to reach a final diagnosis in life, particularly if there are multiple abnormalities, but such diagnoses must be made if the reference source of confirmed diagnoses is to be as unselected as possible. For example, patients with old infarction (and these were mostly 'probable infarctions'; see Appendix B) fulfilled fewer electrocardiographic criteria for infarction; multiple infarctions may conceal individual infarction criteria. All these cases must be included in the reference source if valid estimates of numerical probability are to be given for any diagnosis. Less common conditions, such as right ventricular hypertrophy and emphysema, may complicate such logic.

In Table 7 the optimal lead systems for various diagnoses are presented, based on our current results (Talbot *et al.*, 1973). Left ventricular hypertrophy voltage criteria provide a good example of the value of multiple lead systems since no single system is sufficiently sensitive without producing excessive false-positive results. In isolation the vectorcardiographic criteria of left ventricular hypertrophy were more specific yet as sensitive as the V-lead criteria of left ventricular hyper-

TABLE 7 *Requirements for computer-aided electrocardiogram system*

| *12-lead criteria* | *Frank 3-lead and vectorcardiographic criteria* | *Hybrid 15-lead criteria* |
|---|---|---|
| Axis, hemiblocks | Sensitive diagnosis of left ventricular hypertrophy | Specific diagnosis of anterior infarction ('and-logic') |
| Right bundle-branch system block (complete and incomplete) | Right ventricular hypertrophy | Specific diagnosis (and-logic) and sensitive diagnosis (or-logic) of inferior infarction |
| Anterior ischaemia | | |
| Non-specific abnormalities of ST-T wave | | Left bundle-branch system block |
| | Sensitive diagnosis of anterior infarction | |
| Specific diagnosis of anterior infarction | | Marginal improvements in specific ('and-logic') and sensitive ('or-logic') diagnoses of ischaemia and left ventricular hypertrophy |
| Specific diagnosis of left ventricular hypertrophy | | |
| Anterolateral ischaemia | | |
| Inferior ischaemia | | |
| Lateral infarction | | |

trophy. The most specific criteria were the limb lead criteria of Sokolow and Lyon (1949) with adjustments for the normal limits of QRS voltage that can be expected from axis changes.

We believe that a 15-lead system with hybrid logic does produce better results than either a 12-lead or a 3-lead orthogonal system used alone. A Frank orthogonal system alone does not seem satisfactory for hospital practice though a 12-lead system alone might be sufficient. Multiple leads with vectorcardiographic display are complementary and for optimal diagnosis by a computer electrocardiographic system may be preferred. Other systems of orthogonal leads or praecordial leads may be superior, but redundancy of information will always be important. For diagnostic sensitivity we prefer to combine the 15-lead system and vectorcardiogram with 'or-logic', and for specificity we prefer 'and-logic'. This study has shown that criteria for the diagnosis of infarction and also for the diagnosis of left ventricular hypertrophy or ischaemia are influenced by the presence or absence of other electrocardiographic abnormalities and appropriate weighting should be included in the programme. When clinical information is stored alongside the electrocardiogram, this information may also be used.

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## APPENDIX A

| | *12-lead* | *Frank 3-lead* | *Diagnosis* |
|---|---|---|---|
| | | *Hybrid logic for inferior infarction** | |
| 1) | Q wave of $\geqslant$0·2 mV and $\geqslant$30 ms in II, III, and aVF | — | Inferior infarction |
| 2) | Q wave of $\geqslant$0·2 mV and $\geqslant$30 ms in any 2 leads of II, III, and aVF | Q in Y $\geqslant$0·1 mV or Q/R ratio in Y $\geqslant$0·2 | Inferior infarction |
| 3) | Q wave of $\geqslant$0·2 mV in any 2 leads of II, III, and aVF or Q wave of $\geqslant$0·1 mV and $\geqslant$30 ms in 2 leads of II, III, and aVF | Superior forces $\geqslant$30 ms in frontal plane VCG | Possible inferior infarction |
| 4) | — | Q/R ratio in Y $\geqslant$0·25 and Q wave $\geqslant$30 ms duration | Possible inferior infarction |
| 5) | Q duration $\geqslant$0·1 mV and $\geqslant$20 ms in any 2 leads of II, III, and aVF (if QRS axis $> +60°$) | Q/R ratio in Y $\geqslant$0·2 and Q wave $\geqslant$20 ms duration | Possible inferior wall infection |
| | | *Hybrid logic for anterior infarction** | |
| | *12-lead* | *Frank 3-lead* | *Diagnosis* |
| 1) | No R wave in V1 and V2 and V3, or V3 and V4, or V4 and V5 | — | Anterior infarction |
| 2) | — | Absent Q in Z | Possible anterior infarction |
| 3) | R in V2 and V3 or V3 and V4, or V4 and V5 $\leqslant$0·1 mV | Q/R ratio in Z $<$0·1† or 20 ms initial forces do not enter $+90°$ to $-90°$ in sagittal plane and $0°$ to $+180°$ in horizontal plane VCG | Possible anterior infarction |
| 4) | R in V2 and V3 $\leqslant$0·3 mV | No anterior forces in horizontal and sagittal planes | Possible anterior wall infarction |

*'And-logic' requires the 12-lead criterion and either the orthogonal or vectorcardiographic criterion. 'Or-logic' requires either 12-lead criterion or an orthogonal criterion or a vectorcardiographic criterion.

†Note Q/R ratio in Z only measured if R in Z $>$0·5 mV.

## APPENDIX B

*Definite myocardial infarction*

1) History of increasing angina pectoris and pain for ≥2 hours at rest
    plus
2) Serial AST, LDH, and CK elevation
    plus
3) Elevation of ESR or white blood count
or
4) Coronary arteriographic evidence of occlusion and history of infarction or necropsy confirmation

*Probable myocardial infarction*

1) History of increasing angina pectoris
    plus
2) Final diagnosis of recent or old myocardial infarction

*Definite left ventricular hypertrophy*

1) Precipitating factor: at least one of the following:
    a) Diastolic blood pressure >90 mmHg on 3 or more occasions
    b) Diastolic blood pressure >100 mmHg on 2 occasions
    c) Aortic valve disease or mitral regurgitation
    d) History of hypertension in the past and 1 recording of >90 mmHg diastolic
        plus at least one of the following:
2) a) Severe cardiomegaly clinically or radiographically
    b) Confirmation of suspected lesion by cardiac catheterization
or
3) Evidence of left ventricular hypertrophy or valvular lesion at surgery or necropsy

*Probable left ventricular hypertrophy*

1) As above
    plus
2) Moderate cardiomegaly radiographically or clinically
    or
3) Past history of hypertension or known valvular lesion for at least 5 years

*Abbreviations:* AST—serum aspartate aminotransferase. LDH—serum lactic acid dehydrogenase. CK—creatine kinase.

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# Electrophysiological effects of mexiletine in man[1]

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*The electrophysiological effects of intravenous mexiletine in a dose of 200 to 250 mg given over 5 minutes, followed by continuous infusion of 60 to 90 mg per hour, were studied in 5 patients with normal conduction and in 20 patients with a variety of disturbances of impulse formation and conduction, by means of His bundle electrography, atrial pacing, and the extrastimulus method. In all but 2 patients the plasma level was above the lower therapeutic limit. Mexiletine had no consistent effects on sinus frequency and atrial refractoriness. The sinoatrial recovery time changed inconsistently in both directions; however, of the 5 patients in whom an increase was evident, 3 had sinus node dysfunction. In most patients mexiletine increased the AV nodal conduction time at paced atrial rates and shifted the Wenckebach point to a lower atrial rate. The effective refractory period of the AV node was not consistently influenced, while the functional refractory period increased in 12 out of 14 patients. The HV intervals increased by a mean of 11 ms in 8 patients and were unchanged in 17. Both the relative and effective refractory period of the His-Purkinje system increased after mexiletine. Non-cardiac side effects occurred in 7 out of 25 patients, and cardiac side effects, including one serious, in 2.*

*The results indicate that mexiletine shares some electrophysiological properties with procainamide and quinidine, when given to patients with conduction defects, and that the drug should not be used in patients with pre-existing impairment of impulse formation or conduction. It has additional effects on AV nodal conduction which may be of value in the treatment of re-entrant tachycardias involving the AV node.*

Mexiletine (Kö 1173, 1-(2′,6′-dimethyl-phenoxy)2-aminopropane) is a new antiarrhythmic drug. Its chemical structure and its local anaesthetic properties closely resemble those of lignocaine. It has a strong antiarrhythmic effect in the experimental animal (Allen *et al.*, 1972; Singh and Williams, 1972) and in man (Campbell *et al.*, 1973; Talbot *et al.*, 1973; Talbot, 1975; Campbell *et al.*, 1975). Its clinical interest is based on its effectiveness in lignocaine-resistant arrhythmias (Campbell *et al.*, 1973), its strong antiarrhythmic potency in ouabain-induced arrhythmias in animals (Singh and Williams, 1972) and the feasibility of oral administration (Campbell *et al.*, 1973; Talbot *et al.*, 1973; Campbell *et al.*, 1975; Achuff *et al.*, 1975).

The purpose of this study is to analyse the electrophysiological effects of mexiletine on human cardiac impulse formation and conduction by means of intracardiac electrocardiography.

## Subjects and methods

Twenty-five patients were studied after informed consent had been obtained. Five patients (group A) had entirely normal impulse conduction, 13 patients (group B) had conduction defects in or distal to the His bundle, while in 7 patients (group C) conduction was delayed above the level of the His bundle.

Sinus node dysfunction was the major defect in 10 patients and 3 patients had complete heart block at the time of study. Four patients were studied within 72 hours of the onset of symptoms of acute myocardial infarction. The relevant clinical data are listed in Table 1. No patient was on digitalis treatment and other antiarrhythmic drugs were withheld for at least 24 hours before the time of study.

The study was performed after a light meal; most of the patients received 10 to 20 mg diazepam orally 30 minutes before catheterization.

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[1] Part of this work was presented at the Symposium 'Mexitil in Ventricular Arrhythmias' held in Malta, 7 to 9 April 1976; an abstract of this will be published in *Postgraduate Medical Journal*.

TABLE 1 *Clinical data*

| *Case No.* | *Age (y)* | *Sex* | *Clinical characteristics* | *ECG diagnosis* | *Initial dose of mexiletine (mg)* | *Maintenance dose (mg/h)* | *Plasma level (μg/ml)* | *Side effects* |
|---|---|---|---|---|---|---|---|---|
| *Group A: Normal conduction* | | | | | | | | |
| 1 | 58 | M | Syncope | Within normal limits | 200 mg/5 min | — | 0 96 | None |
| 2 | 74 | M | Syncope | Ventricular extrasystoles | 200 mg/5 min | — | 1·15 | None |
| 3* | 69 | M | Adams-Stokes attacks, old anterior myocard. infarct. | Sinus bradyarrhythmia, atrial flutter | 250 mg/5 min | — | 0 99 | Nausea, vomiting, perspiration |
| 4* | 81 | F | Adams-Stokes attacks | Sinus bradyarrhythmia, sinus arrest, AV junctional rhythm | 250 mg/5 min | 60 | 2 17 | None |
| 5 | 72 | F | Angina, old inferior myocard. infarct. | Normal conduction | 250 mg/5 min | — | 0·72 | Dizziness, nausea, vomiting, visual disturbance |
| *Group B: Infra-His conduction delay* | | | | | | | | |
| 6 | 76 | F | Angina | LBBB, ventricular extrasystoles | 250 mg/5 min | — | — | None |
| 7 | 76 | M | Recent anterior myocard. infarct. | RBBB, left anterior hemiblock | 250 mg/5 min | 90 | 4·2 | None |
| 8 | 67 | F | Dizziness | Sinus bradyarrhythmia, atrial fibrillation, LBBB, RBBB | 250 mg/5 min | 90 | 6·2 | None |
| 9* | 65 | F | Adams-Stokes attacks | Brady-tachycardia syndrome, atrial fibrillation | 250 mg/5 min | 90 | 0·74 | Nausea |
| 10 | 33 | M | Adams-Stokes attacks | Complete heart block | 250 mg/5 min | 90 | 0·66 | None |
| 11 | 88 | F | Dizziness, intestinal haemorrhage | RBBB, LBBB, Mobitz-II block | 125 mg/5 min | 30 | 1·4 | None |
| 12* | 81 | F | Dizziness | 2:1 sinoatrial block | 250 mg/5 min | 60 | 1·1 | Nausea, vomiting, dizziness, nystagmus |
| 13 | 52 | M | Fatigue | Atrial fibrillation, complete AV block, LBBB | 250 mg/5 min | 60 | 0·86 | None |
| 14 | 74 | M | Syncope | RBBB, left anterior hemiblock | 250 mg/5 min | 60 | 0·96 | None |
| 15 | 59 | M | Recent inferior myocard. infarct. | RBBB | 250 mg/5 min | 60 | — | None |
| 16 | 54 | M | Angina, recent myocard. infarct. | Rate-dependent RBBB | 200 mg/5 min | 60 | 0·78 | None |
| 17* | 56 | F | Dizziness, syncope | Sinus bradyarrhythmia, left anterior hemiblock | 200 mg/5 min | — | 1·28 | Diplopia |
| 18 | 78 | F | Asymptomatic | Intermittent 5:1 AV block | 200 mg/5 min | — | 0·55 | None |
| *Group C: Supra-His conduction delay* | | | | | | | | |
| 19* | 77 | M | Syncope, gastro-intestinal haemorrhage | Sinus bradyarrhythmia | 250 mg/5 min | 90 | 2 0 | None |
| 20* | 70 | M | Asymptomatic | Brady-tachycardia syndrome, LBBB | 250 mg/5 min | 1300** | — | None |
| 21 | 80 | F | Adams-Stokes attacks | 1st degree AV block | 250 mg/5 min | 90 | 1·54 | Nausea |
| 22 | 62 | M | Syncope | 1st degree AV block | 250 mg/5 min | 60 | 0·92 | None |
| 23* | 59 | M | Recent inferior myocard. infarct. | Complete AV block, AV junctional rhythm, sinus arrest | 250 mg/5 min | 60 | 0·46 | Asystolic arrest |
| 24* | 75 | F | Mitral stenosis and regurgitation | Atrial quiescence | 250 mg/5 min | 60 | 1·33 | Nausea, vomiting dizziness, visual disturbance |
| 25* | 50 | M | Dizziness | 1st degree AV block, carotid hypersensitivity | 200 mg/5 min | 60 | 0·28 | None |

LBBB, left bundle-branch block; RBBB, right bundle-branch block.
*, patients with the sick sinus syndrome.
**, this patient accidentally received an additional 250 mg mexiletine in 11 minutes instead of the usual maintenance infusion.

After local analgesia with 100 mg lignocaine, two electrode catheters were introduced into the right femoral vein. A tripolar electrode wire was positioned against the high lateral wall of the right atrium. The two distal electrodes were used for bipolar atrial pacing, the proximal electrode for the recording of a unipolar high right atrial electrogram.

Another tripolar electrode wire, with electrodes 10 mm apart, was positioned across the tricuspid valve in the His bundle region, as described by Scherlag *et al.* (1969). Standard leads I, II, III, a unipolar high right atrial electrogram, and a His bundle electrogram were recorded on an 8-channel Elema recorder at a paper speed of 100 mm/s. Refractory periods were measured by the extrastimulus technique with a modified Medtronic pulse generator (5837), delivering a premature beat with a variable coupling interval after every eighth beat of the basic driven cycle. All stimuli were delivered at twice diastolic threshold and a pulse duration of 2 ms. The atrium was driven at increasing rates with steps of 10 beats/min, beginning with a frequency as close as possible to the spontaneous sinus rate, until a rate of 200/min was reached or high degree AV block appeared. The mean sinoatrial recovery time was calculated from 5 successive determinations.

TABLE 2 *Conduction intervals before and after mexiletine*

| *Case No.* | *Basic cycle length (ms)* | *PA (ms)* | | *AH (ms)* | | *HV (ms)* | | *HS (ms)* | | *Wenckebach point* | | *Pooled AH* | | *Pooled HV* | | *Sino-atrial recovery time** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Before* | *After* | *Before* | *After* | *Before* | *After* | *Before* | *After* | *Before* | *After* | *Before* | *After* | *Before* | *After* | *Before* | *After* |
| *Group A: Normal conduction* | | | | | | | | | | | | | | | | | |
| 1 | 720 | 70 | 70 | 140 | 135 | 45 | 45 | 140 | 150 | 140 | 150 | 1420 | 1405 | 405 | 405 | 1106 | 990 |
| 2 | 650 | 50 | 50 | 145 | 145 | 35 | 40 | 145 | 150 | 140 | 150 | 1435 | 1415 | 270 | 285 | 1400 | 1298 |
| 3† | 750 | 70 | 70 | 95 | 90 | 45 | 55 | 135 | 145 | >180 | 150 | 905 | 995 | 360 | 400 | ** | 3287 |
| 4† | 650 | 45 | 40 | 90 | 100 | 40 | 40 | 130 | 130 | 170 | 150 | 1070 | 1225 | 400 | 400 | 1284 | 1184 |
| 5 | 810 | 30 | 50 | 85 | 85 | 50 | 50 | 150 | 155 | 150 | 150 | 1255 | 1430 | 450 | 470 | 1552 | 1400 |
| *Group B: Infra-His conduction delay* | | | | | | | | | | | | | | | | | |
| 6 | 900 | 50 | ** | 90 | ** | 55 | 55 | 225 | 235 | ** | ** | ** | ** | ** | ** | ** | ** |
| 7 | 750 | 30 | 30 | 90 | 90 | 65 | 65 | 165 | 170 | 130 | 130 | 1150 | 1420 | 520 | 520 | 1030 | 950 |
| 8 | 700 | 20 | ** | 120 | ** | 65 | 85 | 240 | ** | ** | ** | ** | ** | ** | ** | ** | ** |
| 9† | 260‡ | ** | ** | ** | ** | 45 | 60 | 145 | 200 | ** | ** | ** | ** | ** | ** | ** | ** |
| 10 | 720 | 30 | 30 | 80 | 80 | ~ | ~ | ~ | ~ | 140 | 140 | 955 | 985 | — | — | 1146 | 1090 |
| 11 | 700 | 50 | 50 | 80 | 80 | 60–110 | 75–130 | 180–230 | 190–250 | 170 | 140 | 750 | 745 | 120 | 160 | 998 | 835 |
| 12† | 700 | 40 | 40 | 100 | 100 | 60 | 60 | 140 | 140 | 190 | 160 | 1125 | 1180 | 720 | 780 | 1348 | 1756 |
| 13 | 240‡ | ** | ** | ** | ** | 60 | 70 | 220 | 230 | ** | ** | ** | ** | ** | ** | ** | ** |
| 14 | 900 | 35 | 35 | 80 | 80 | 40 | 40 | 160 | 160 | 120 | 120 | 1175 | 1195 | 440 | 440 | 1354 | 1355 |
| 15 | 550 | 30 | 30 | 80 | 80 | 40 | 40 | 150 | 155 | >190 | >190 | 955 | 930 | 360 | 415 | 828 | 762 |
| 16 | 610 | 50 | 50 | 90 | 90 | 60 | 60 | 180 | 185 | >190 | >190 | 1206 | 1245 | 600 | 600 | 886 | 816 |
| 17† | 960 | 50 | 50-90 | 120 | 115 | 50 | 50 | 150 | 150 | 100 | 100 | 1130 | 1215 | 350 | 350 | 1286 | 1430 |
| 18 | 650 | 50 | 50 | 105 | 115 | 55 | 55 | 130 | 130 | 170 | 150 | 965 | 1130 | 330 | 330 | 1074 | 988 |
| *Group C: Supra-His conduction delay* | | | | | | | | | | | | | | | | | |
| 19† | 750 | 30–50 | 50 | 160 | 150 | 50 | 50 | 170 | 170 | 120 | 160 | 1490 | 1535 | 400 | 400 | 1474 | 1562 |
| 20† | 830 | 40 | ** | 230 | ** | 75 | 75 | 235 | 250 | ** | ** | ** | ** | ** | ** | ** | ** |
| 21 | 750 | 50 | 50 | 190 | 170 | 50 | 50 | 125 | 125 | 100 | 80 | 420 | 460 | 100 | 100 | 1110 | 1302 |
| 22 | 800 | 40 | 40 | 170–255§ | 195–205§ | 50§ | 50§ | 135§ | 145§ | 150 | 140 | — | — | — | — | 1286 | 1216 |
| 23† | 700 | 30 | 30 | ~ | 140–250 | 35 | 35 | 110 | 110 | <80 | ¶ | ¶ | ¶ | ¶ | ¶ | 4480 | ¶ |
| 24† | 680 | †† | †† | †† | 550 | 50 | 60 | 140 | 150 | †† | 110 | †† | †† | †† | †† | †† | †† |
| 25† | 650 | 50 | 50 | 170 | 180 | 55 | 60 | 140 | 150 | 130 | 110 | 1055 | 1325 | 330 | 360 | 930 | 1158 |

*Mean of 5 determinations.

†Patients with the sick sinus syndrome.

‡Spontaneous atrial cycle length (ms).

§$AH_2$, $H_2V$, and $H_2S$ intervals in Case 22 with split His bundle deflection (see text).

¶No values because of complete heart block and loss of atrial capture after mexiletine.

**No values because of atrial arrhythmias.

††No values because of atrial quiescence and absence of atrial capture.

~ No values because of complete heart block.

After completion of control measurements, 200 to 250 mg mexiletine was infused intravenously at a constant rate over a 5 minute period, followed by a maintenance infusion of 60 to 90 mg per hour. The dose each patient received is listed in Table 1. All measurements were repeated and completed within 20 minutes after the beginning of the infusion. One or more venous blood samples were obtained during the study for plasma mexiletine determination by gas-liquid chromatography, using a modification of the method described by Kelly *et al.* (1973).

## Definition of terms

*PA interval:* time in ms between the stimulus artefact and the first sharp deflection of the P wave on the His bundle electrogram (normal 20 to 50 ms).

*AH interval:* time between the onset of the P wave on the His bundle electrogram and the onset of the His spike (normal 60 to 140 ms).

*HV interval:* time between the onset of the His spike and the onset of the QRS complex in the standard leads (normal 30 to 55 ms).

*HS interval:* time between the onset of the His spike and the end of the QRS complex in the standard leads (normal 100 to 145 ms).

*Pooled AH intervals:* sum in ms of the AH times at each driven atrial rate with 1:1 or 2:1 AV conduction.

*Pooled HV intervals:* sum in ms of the HV intervals of each driven atrial rate with 1:1 conduction.

*Wenckebach point:* the highest driven atrial rate permitting 1:1 conduction. In patients with the Wenckebach phenomenon while in sinus rhythm the highest driven atrial rate permitting 2:1 conduction was taken as Wenckebach point.

*Sinoatrial recovery time:* the interval in ms between the last pacemaker spike and the first spontaneous P wave after abruptly turning off the external pacemaker 20 s after atrial pacing at a rate of 120/min (normal 954±196 (SD) ms).

*Effective refractory period of the atrium* ($ERP_a$)*:* the longest $S_1$-$S_2$ interval at which $S_2$ does not propagate into the atrium.

*Effective refractory period of the AV node* ($ERP_{avn}$)*:*

TABLE 3 *Effects of mexiletine on refractory periods in 17 patients*

| *Case No.* | *Basic cycle length (ms)* | $ERP_a$ *Before* | *After* | $ERP_{avn}$ *Before* | *After* | $FRP_{avn}$ *Before* | *After* | $RRP_{hps}$ *Before* | *After* | $ERP_{hps}$ *Before* | *After* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Group A: Normal conduction* | | | | | | | | | | | |
| 1 | 720 | <300 | <320 | 340 | 340 | 470 | 450 | ‡ | ‡ | ‡ | ‡ |
| 2 | 650 | 230 | 240 | 330 | 315 | 460 | 465 | ‡ | ‡ | ‡ | ‡ |
| 3* | 750 | 335 | 350 | § | § | 420 | 430 | <420 | 480 | ‡ | ‡ |
| 4* | 650 | 250 | 250 | 300 | 295 | 390 | 400 | ‡ | ‡ | ‡ | ‡ |
| 5 | 810 | 295 | 320 | ≤340 | ≤370 | 475 | 485 | § | § | § | § |
| *Group B: Infra-His conduction delay* | | | | | | | | | | | |
| 10 | 720 | 300 | 270 | § | 290 | ≤445 | 480 | ‡ | ‡ | ‡ | ‡ |
| 11† | 700 | 290 | 250 | <310 | <310 | ≤420 | ≤430 | 520 | 680 | 420 | 570 |
| 12* | 700 | 260 | 290 | 315 | ≤335 | ≤380 | ≤410 | 405 | 470 | ‡ | ‡ |
| 14 | 900 | 270 | 270 | <340 | 330 | 515 | 490 | § | ‡ | § | ‡ |
| 15 | 550 | 220 | 240 | <240 | <250 | 330 | 350 | <330 | 550 | § | § |
| 16 | 610 | ≤230 | ≤230 | ≤240 | ≤265 | 335 | 335 | § | § | § | § |
| 17* | 960 | 320 | 360 | 525 | 440 | 575 | 580 | ‡ | ‡ | ‡ | ‡ |
| 18 | 650 | 200 | 220 | 275 | 280 | 370 | 390 | 390 | 520 | 375 | 475 |
| *Group C: Supra-His conduction delay* | | | | | | | | | | | |
| 19* | 750 | 270 | 300>250 | 440 | 500 | 560 | 610 | ‡ | ‡ | ‡ | ‡ |
| 21 | 750 | 310 | 280 | 470 | 475 | 645 | 655 | ‡ | ‡ | ‡ | ‡ |
| 22 | 800 | 330 | 310 | ** | <340 | ** | ** | ≥790 | ** | ≥790 | ** |
| 23* | 700 | 360 | | >750 | ¶ | >750 | ¶ | ‡ | ‡ | ‡ | ‡ |
| 25* | 650 | 265 | 240 | 360 | 415 | 515 | 580 | ‡ | ‡ | ‡ | ‡ |

*Patients with the sick sinus syndrome.

†Because of 2:1 block distal to H the actual hps-refractoriness is >700 ms (basic paced cycle): the intervals presented were measured only when last beat of basic cycle before extra stimulus was blocked distal to H.

‡Study limited by AV nodal refractoriness.

§Study limited by atrial refractoriness.

¶Not performed because of complete AV nodal block and loss of atrial capture.

**Not obtained because of antegrade conduction bypassing the AV node.

Abbreviations as in text: see 'Definition of terms'.

the longest $A_1$-$A_2$ interval at which $A_2$ fails to reach the His bundle.

*Functional refractory period of the AV node ($FRP_{avn}$):* the shortest interval between $H_1$ and $H_2$, both of which are conducted from the atrium.

*Effective refractory period of the His-Purkinje system ($ERP_{hps}$):* the longest $H_1$-$H_2$ interval at which $H_2$ fails to conduct to the ventricles.

*Relative refractory period of the His-Purkinje system ($RRP_{hps}$):* the longest $H_1$-$H_2$ interval at which $H_2$ conducts to the ventricles with a longer HV interval and/or with an aberrant QRS complex.

## Results

In Table 2 conduction intervals during atrial stimulation as close as possible to the spontaneous sinus rate before and after mexiletine are listed, together with the pooled AH intervals, pooled HV intervals, sinoatrial recovery time, and Wenckebach point during atrial pacing.

Table 3 summarizes the effects of mexiletine on the refractoriness of the His-Purkinje system, AV node, and atrium. Measurement of refractoriness was impossible in 1 patient because of atrial flutter and complete AV block, in another patient because of atrial quiescence with absence of atrial electrical activity, and in 4 patients because of atrial arrhythmias. In 1 patient (Case 7) only control values are available because of atrial flutter induced by an extrastimulus.

Interference with the results by the local anaesthesia with 100 mg lignocaine is unlikely, as has been shown earlier (Schwartz *et al.*, 1974; Roos and Dunning, 1975).

### Sinus node function

In 15 patients sinus rate could be measured before, during, and immediately after the infusion of mexiletine.

The mean rate before mexiletine was 73·1 ±13·0 (SD) and after mexiletine 75·3 ±12·4. This difference has no statistical significance. Atrial refractoriness (Fig. 1, Table 3) was not consistently affected by mexiletine. In 6 patients a mean increase of 24 ms occurred, in 2 patients there was no change, and in 6 patients atrial refractoriness decreased by a mean of 25 ms. The mean net change in all patients was –0·35 ms (not statistically significant).

The sinoatrial recovery time is an indicator of sinus node function and was recorded before and after mexiletine in 17 patients (Table 2). In 5 patients it increased (significantly in 1) and in 11 patients it decreased (significantly in 4). The mean sinoatrial recovery time before and after mexiletine was exactly the same (1181 ms ±211 and 1181 ±274 ms, respectively). Of the 5 patients who showed an increase after mexiletine, 3 had the sick sinus syndrome, and in only 1 patient with this syndrome did mexiletine decrease the sinoatrial recovery time.

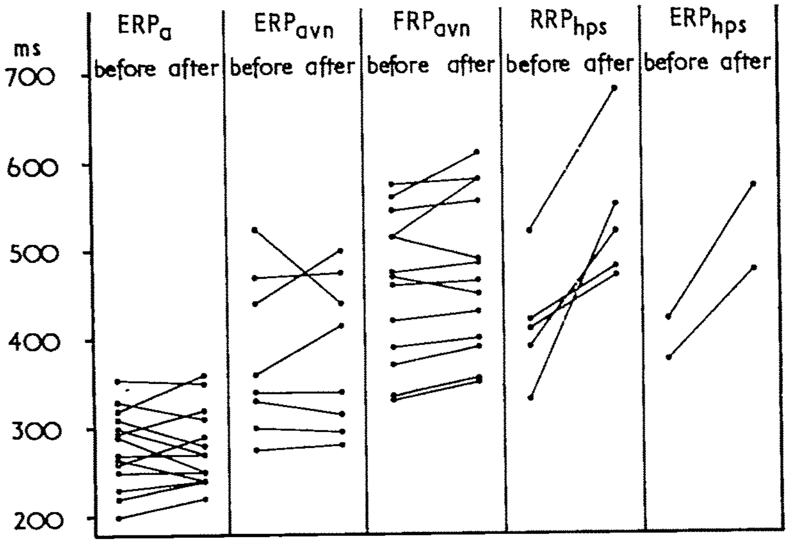

FIG. 1 *Refractory periods of the atrium, AV node, and His-Purkinje system before and after intravenous mexiletine. Abbreviations as in text: see 'Definition of terms'.*

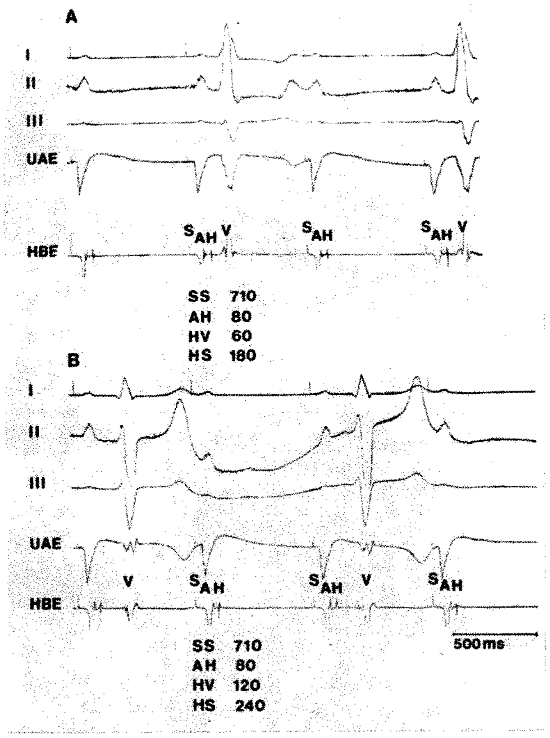

FIG. 2 *Case 11. Panel A shows a paced atrial rate (cycle length 710 ms) with 2:1 HV block before mexiletine. The conducted beats show complete left bundle-branch block with a HV interval of 60 ms. Panel B shows the same paced atrial rate after intravenous mexiletine. Again 2:1 HV block is present, but now right bundle-branch block with left anterior hemiblock is present, with considerable prolongation of the HV interval to 120 ms in the conducted beats. I, II, III: standard limb leads; A: atrial wave; AH: AH interval (ms); H: His bundle deflection; HBE: His bundle electrogram; HS: total intraventricular conduction (ms); HV: HV interval (ms); S: stimulus artefact; SS: interval between two atrial stimuli (ms); UAE: unipolar atrial electrogram.*

## AV nodal conduction

The AH interval, as measured during atrial pacing at a rate as close as possible to the spontaneous sinus frequency (Table 2) decreased in 5 patients (mean –9 ms), increased in 3 (mean +10 ms), and was unchanged in 8. The mean net change was –0·3 ms (not statistically significant). During atrial pacing, however, at increasing rates, the AH interval tended to become more prolonged after mexiletine. Thus, the pooled AH intervals (Table 2) increased in 12 patients, though in 5 patients a slight decrease was observed. The mean change after mexiletine was +8 per cent. In 3 patients the Wenckebach point occurred at a higher atrial rate, in 5 patients it remained unchanged, and in 8 patients it was reached at a lower paced atrial rate (Table 2).

The effective refractory period of the AV node was not consistently influenced by mexiletine (Table 3, Fig. 1). In 4 patients the change was 5 ms or less, in 2 patients the ERP increased (mean 50 ms) and in 2 others it decreased (mean 57 ms). The mean net change was +2·5 ms (not statistically significant). The functional refractory period of the AV node increased more consistently in 11 patients (mean +21·8 ms) and decreased in 2 (mean –22·5 ms); the mean net change was +14·2 ms, but was not statistically significant.

## His-Purkinje conduction

Of the 5 patients with normal conduction, 2 showed a minimal increase of the HV interval after mexiletine (+5 and +10 ms). One of these also showed a slight increase of the relative refractory period of the His-Purkinje system (Table 3). Six other patients showed an increase of the HV conduction time. Four of these had infra-His conduction defects (mean increase +15 ms) and 2 supra-His conduction delay (mean increase +7·5 ms) (Table 2). The mean increase of the HV interval was 3·3 ms, which was not statistically significant. In the 5 patients in whom the relative refractory period of the His-Purkinje system could be measured, a consistent and statistically significant increase (mean +127 ms, $P < 0\cdot05$) was found after mexiletine. Four of these patients had infra-His conduction disturbances. In 2 patients (also with conduction delay below the His bundle) the effective refractory period of the His-Purkinje system increased (mean +125 ms). Some of the electrophysiological responses of these patients to mexiletine are illustrated in Fig. 2 and 3. Fig. 4 shows the effects of mexiletine on an antegrade AV nodal bypass tract in a patient with an intra-His conduction defect; the effective refractory period of this tract increased from 340 to 680 ms after mexiletine.

## Complete heart block

Of the 3 patients with complete heart block, the effects of mexiletine could be assessed in 2, the third being completely pacemaker dependent. In Case 13, who had complete AV nodal block, the frequency of the AV junctional escape rhythm was not changed by mexiletine. The second patient (Case 23), also with complete AV nodal block, had a period of

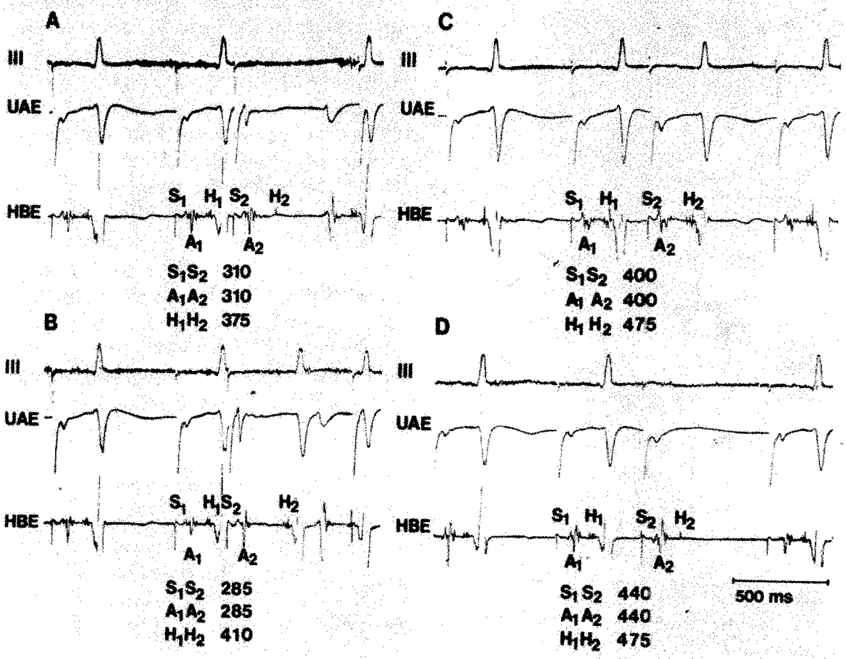

FIG. 3 *Case 18. Panel A shows the effective refractory period of the His-Purkinje system (H1–H2 = 375 ms) before mexiletine. Panel B shows a gap phenomenon: a premature beat with a shorter coupling interval than in panel A (285 ms) is now conducted to the ventricles because the H1-H2 interval increases to 410 ms because of functional AV nodal refractoriness. Panel D shows an increased effective refractory period of the His-Purkinje system (475 ms) after intravenous mexiletine. Panel C shows that before mexiletine a premature beat with the same H1-H2 interval of 475 ms is conducted to the ventricles. The basic cycle length in all panels is 650 ms. The His bundle deflection is fragmented, showing 3 separate spikes in all conducted beats; the blocked beats show only 1 spike, indicating intra-His conduction disturbance. Abbreviations and symbols as in Fig. 2.*

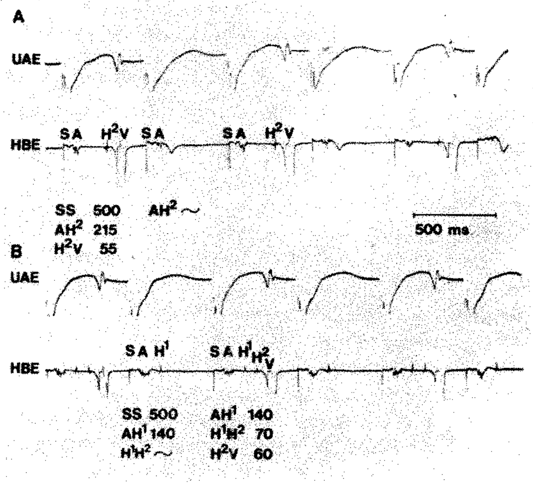

FIG. 4 *Case 22. Panel A shows a paced atrial rhythm with a cycle length of 500 ms before mexiletine. There is apparent 2:1 AV nodal block; however, when the cycle was shortened to a critical length of 400 ms (not shown in figure) a split His bundle deflection ($H^1$ and $H^2$) appeared with a stable $AH^1$ interval of 160 ms, indicating normal AV nodal conduction and 2:1 intra-His block; apparently an AV nodal bypass tract existed (James bundle) which became refractory at a critical cycle length of 400 ms. Panel B shows the same cycle length of 500 ms after intravenous mexiletine. Because of refractoriness of the AV nodal bypass tract, conduction takes place through the AV node, unmasking a 2:1 intra-His block (every second beat being blocked distal to $H^1$), with a normal $AH^1$ interval at this rate of 140 ms. Abbreviations and symbols as in Fig. 2.*

14 s total cardiac standstill after mexiletine; this patient is described in greater detail below.

### Plasma mexiletine levels

Eighteen patients received an intravenous loading dose of 250 mg mexiletine in 5 minutes, followed by a continuous infusion of 60 to 90 mg per hour. The plasma levels at the time of study ranged from 0·46 to 6·2 μg/ml (mean 1·65 ±0·40 (SEM)). Six patients received a loading dose of 200 mg in 5 minutes, followed by a maintenance infusion of 60 mg per hour. The plasma levels ranged from 0·28 to 1·15 μg/ml (mean 0·83 ±0·14). Therapeutic plasma levels range from 0·5 to 2·0 μg/ml (Talbot *et al.*, 1973). Two of our patients had plasma levels less than 0·5 μg/ml, and 2 had toxic levels (>3 μg/ml); all other patients had plasma levels within the therapeutic range.

### Side effects

Eight patients suffered from side effects; 7 of them had received the higher loading dose of 250 mg in 5 minutes. Nausea was the most frequent symptom (6 out of 8 patients), followed by dizziness (3/8), vomiting (3/8), and visual disturbances (3/8), namely nystagmus, diplopia, and blurred vision. This high frequency of side effects is related to the dose and the rapidity with which the drug was injected. Fig. 5 shows that when 250 mg mexiletine is injected in 5 minutes, the plasma level immediately after completion of the injection is above the upper therapeutic limit and clearly in the toxic range. During the next minutes the plasma levels rapidly come down to within the therapeutic range.

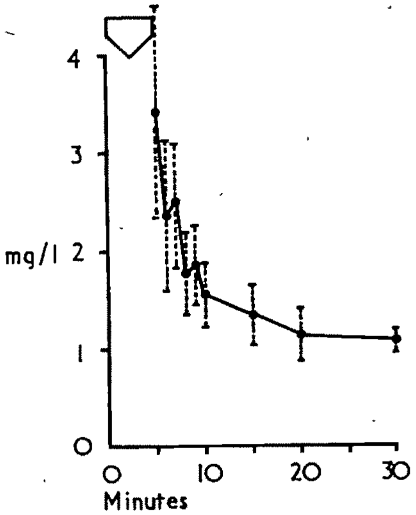

FIG. 5 *This figure shows the mean plasma mexiletine levels (± SEM) in 5 patients receiving 250 mg intravenously in 5 minutes, followed by a maintenance infusion of 90 mg/hour. Note that immediately after completion of the injection the plasma level is in the toxic range (>3 μg/ml).*

One patient (Case 23) had serious cardiac side effects. This patient was studied 48 hours after the onset of symptoms of acute inferior myocardial infarction, complicated by complete AV nodal block, with periods of sinus arrest and AV junctional escape rhythm. At the time of study complete heart block was present. During injection of mexiletine a Wenckebach type of block in the AV node developed, suggesting improved AV nodal conduction. Six and a half minutes after the beginning of the injection there was sudden cardiac standstill lasting for a period of 14 seconds, followed by a ventricular escape beat. Right ventricular pacing was then instituted and after 8 minutes the P waves returned. The plasma level at the time of this event was only 0·46 μg/ml, which is no more than the lower limit of the therapeutic range. Though this may have been coincidence, the sequence of events suggests that the injection of mexiletine was responsible for asystole in this case. Another patient (Case 12) with 3:2 sinoatrial block showed a reduction in the number of sinus beats from an average of 73 beats/min before to 40 beats/min 30 minutes after mexiletine, with periods of sinus arrest up to 3 seconds.

## Discussion

An ideal antiarrhythmic drug, that is effective, easy to administer, and without side effects and toxic reactions has not yet been produced. Lignocaine, probably the least toxic and certainly the most widely used drug in the coronary care unit, is not always effective and should be used cautiously in patients with distal conduction defects (Roos and Dunning, 1975); and it cannot be given orally. Procainamide, quinidine, phenytoin, and β-adrenergic blocking drugs, all of which can be administered orally, have more side effects than lignocaine, and especially in the long-term treatment of arrhythmias the incidence of adverse reactions is high. There is, therefore, a need for additions to our therapeutic armamentarium.

Mexiletine, originally developed as an anticonvulsant drug, has been studied in animals and in a limited number of patients. In animals (Allen *et al.*, 1972; Singh and Williams, 1972) mexiletine was effective in ventricular arrhythmias and especially in those provoked by ouabain. In the isolated rabbit atrium mexiletine reduced the maximum frequency with which the atrium could be driven, raised the threshold for electrical stimulation, slowed conduction velocity, and depressed contraction. The drug reduced the maximum rate of rise of the action potential of rabbit atrial and ventricular muscle. The resting potential and action potential duration were not affected.

In the clinical studies of Campbell *et al.* (1973), Talbot *et al.* (1973), Campbell *et al.* (1975), and Achuff *et al.* (1975), mexiletine appeared to be effective against ventricular arrhythmias, both after acute myocardial infarction and in patients with chronic arrhythmias. When lignocaine failed, mexiletine was often successful. After intravenous administration a high percentage of patients had unacceptable side effects. On the other hand, mexiletine, when given orally, compared favourably with procainamide with respect to toxicity and was equally effective (Campbell *et al.*, 1975).

In this study, designed to analyse the electrophysiological properties of mexiletine, we did not find consistent effects on the spontaneous sinus rate at therapeutic plasma levels. Small and inconsistent changes in both directions of atrial refractoriness were found and the same was true for sinoatrial recovery times. No appreciable changes were found in atrial conduction time. Two patients, however, showed a striking reduction or even total absence of sinus activity after mexiletine. Both had pre-existent sinus node dysfunction. In animal experiments, mexiletine has been shown to cause sinus bradycardia, and bradyarrhythmias were described in man as a side effect (Campbell *et al.*, 1973; Talbot *et al.*, 1973). A possible explanation for the fact that sinus node function was not influenced by mexiletine in 23 of the 25 patients studied, could be that the drug has both a vagolytic activity and an intrinsic depressant effect. Such effects work in opposite directions and the net result depends on which of the two is stronger in an individual patient. Patients with sinus node dysfunction are known to respond to atropine-like drugs with only minimal increase in sinus frequency, and it is plausible that in these patients a depressant effect of mexiletine would become manifest.

Conduction time through the AV node was not influenced by mexiletine at driven atrial rates close to the spontaneous sinus rate. However, at higher frequencies the pooled AH times tended to increase and the Wenckebach point shifted to a lower atrial rate in the majority of the patients. The effective refractory period of the AV node changed only slightly, and in both directions, while AV nodal functional refractoriness increased. Measurements of the three variables reflecting AV nodal conduction (functional refractory period, Wenckebach point, and pooled AH intervals) were available in 14 patients before and after mexiletine. In 11 out of these 14 patients, 2 or 3 of these measurements indicated depressed conduction after mexiletine; in 2 patients the Wenckebach point was unchanged, while the 2 other variables changed in opposite directions; in only 1 patient did all 3 measurements indicate improved conduction. The exact mechanism by which mexiletine influences AV nodal function is not clear. The net effect in the majority of patients, both with normal and abnormal AV nodal conduction, is decreased conduction. Again this may be the resultant of a vagolytic and an (in most of the patients apparently dominating) intrinsic depressant action. In Case 23 the sequence of events (improved AV nodal conduction followed by cardiac standstill) is consistent with the view that mexiletine has such a dual action. The net effect of mexiletine on AV nodal conduction could be of value in the treatment of re-entrant tachycardias involving the AV node. Its possible usefulness in tachycardias associated with pre-excitation is illustrated by one patient in our study (Fig. 5). Two patients in this study, with atrial tachycardias occurring during catheterization, reverted to sinus rhythm after mexiletine; another patient, not in this study, with paroxysmal supraventricular tachycardia, resistant to all conventional drugs, has now been free of attacks for 1½ years on treatment with oral mexiletine.

In this study mexiletine appeared to produce a small increase in total intraventricular conduction time in the majority of the patients. In some patients (most of them with pre-existing infra-His conduction defects) the HV interval increased and/or His-Purkinje refractoriness increased. These results are in agreement with those of Lang, Just, and Limbourg (1975), who also found delayed infra-His conduction in some of their patients. In this respect, mexiletine resembles procainamide (Josephson *et al.*, 1974a) and quinidine (Josephson *et al.*, 1974b) and should be classified as a class IA antiarrhythmic drug (Singh and Hanswirth, 1974). McComish *et al.* (1975), however, found, in patients with normal cardiac conduction, a slight but statistically significant decrease of the relative refractory period of the His-Purkinje system after mexiletine.

The mechanism by which mexiletine exerts its antiarrhythmic effect thus seems to be a complicated one. It seems likely that mexiletine, like lignocaine, acts differently on normal and diseased conduction tissue.

Like Campbell *et al.* (1973) and Talbot *et al.* (1973) we found a high incidence of side effects after intravenous injection of mexiletine (8 out of 25 patients). Two patients had a cardiotoxic reaction which was severe in one of these. Seven of the 8 patients who suffered from side effects had received the higher dose of 250 mg infused over 5 minutes, while only 1 patient, who received 200 mg in 5 minutes, showed mild symptoms (diplopia). The side effects were thus related to the dose and the rapidity of intravenous injection and were confined to a period of 5 to 20 minutes after the loading dose was given.

Like Talbot *et al.* (1973) our experience with oral mexiletine indicates that side effects do not occur or only rarely do so with this route of administration. The apparent effects on intracardiac conduction and the described adverse effects in 2 patients make the drug less suitable for treatment of patients with pre-existing disturbances of impulse formation and/or infra-His conduction.

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# Effect of sublingual nitroglycerin on cardiac performance in patients with coronary artery disease and non-dyskinetic left ventricular contraction

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*In 8 patients with coronary artery disease and symmetrical left ventricular contraction, an echocardiographic study of left ventricular function was performed before and 3 minutes after the administration of 0·6 mg nitroglycerin sublingually. The left ventricular end-diastolic diameter decreased from* $5{\cdot}2\pm0{\cdot}2$ *to* $4{\cdot}9\pm0{\cdot}2$ *cm* ($P<0{\cdot}05$) *and the end-systolic diameter from* $4{\cdot}2\pm0{\cdot}2$ *to* $3{\cdot}7\pm0{\cdot}2$ *cm* ($P<0{\cdot}001$). *The estimated stroke volume did not change significantly, while the cardiac output increased,* $5{\cdot}8\pm0{\cdot}6$ *to* $7{\cdot}7\pm0{\cdot}6$ $l\,min^{-1}$ ($P<0{\cdot}001$) *and the heart rate increased from* $72\pm5$ *to* $90\pm6$ ($P<0{\cdot}001$). *The mean arterial blood pressure decreased from* $105\pm4$ *to* $88\pm3$ *mmHg* ($P<0{\cdot}001$). *The ejection fraction increased from* $53\pm3$ *per cent to* $65\pm6$ *per cent* ($P<0{\cdot}001$) *and the mean velocity of circumferential fibre shortening* ($V_{CF}$) *from* $0{\cdot}81\pm0{\cdot}05$ *to* $1{\cdot}15\pm0{\cdot}10$ *circumferences per second* ($P<0{\cdot}001$). *The estimated midsystolic midwall stress decreased from* $155\pm14\,g\,cm^{-2}$ *to* $102\pm12\,g\,cm^{-2}$ *after nitroglycerin* ($P<0{\cdot}001$).

*The administration of nitroglycerin was associated with a significant decrease in left ventricular preload and afterload. A vasodilating effect is suggested by the fall in peripheral resistance. The overall improvement in ejection fraction and* $V_{CF}$ *may not reflect a true increase in contractility, because of the concomitant fall in wall stress.*

Although nitrites have been used for more than a century for the relief of angina pectoris (Brunton, 1867), there is still considerable controversy surrounding their exact mode of action. It is uncertain whether nitroglycerin acts chiefly by coronary vasodilatation (Fam and McGregor, 1964; Becker, Fortuin, and Pitt, 1971; Cohen *et al.,* 1973; Goldstein, Stinson, and Epstein, 1973), or by the reduction of myocardial oxygen demands (Mason and Braunwald, 1965; Frick *et al.,* 1968; Ganz and Marcus, 1972). The myocardial oxygen consumption is principally dependent on three variables, the left ventricular wall stress, the heart rate, and the contractile state of the heart (Braunwald, 1971). The left ventricular systolic wall stress, or afterload, is in turn determined by the intracavitary systolic blood pressure, chamber size, and wall thickness.

Echocardiography is a reliable method for estimating left ventricular minor axis, particularly in serial studies, using a patient as his own control (Pombo, Troy, and Russell, 1971; Fortuin *et al.,* 1971; Gibson, 1973; Redwood, Henry, and Epstein, 1974). Though two recent investigations have shown a decrease in the echographic left ventricular dimension after nitroglycerin administration (DeMaria *et al.,* 1974; Burggraf and Parker, 1974), no reports have been published about its effects on estimated wall stress in man. In the present study, changes in left ventricular afterload after nitroglycerin were estimated, using calculations based on a thick-wall spherical model of the chamber. This method probably allows a closer assessment of changes in myocardial oxygen demand than pressure and volume measurements alone. Changes in afterload can then be correlated with concurrent changes in heart rate and in the mean velocity of internal dimension shortening, used as an index of contractility, thus providing an estimate of all three major determinants of myocardial oxygen consumption.

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TABLE

| *Case No.* | *Age (y)* | *BSA ($m^2$)* | *Cardiac output* ($l\ min^{-1}$)* | *Pressures (mmHg)* | | | *Coronary arteries†* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *LV* | *Aorta* | *PA* | *LAD%* | *LC%* | *RCA%* |
| 1 | 53 | 0·02 | 4·7 | 200/25 | 200/100 | 21/9 | 75 | 75 | 95 |
| 2 | 50 | 1·94 | 4·6 | 125/19 | 125/65 | 20/5 | 75 | 100 | 75 |
| 3 | 65 | 1·76 | 3·6 | 175/15 | 175/90 | 18/5 | 25 | 100 | 95 |
| 4 | 64 | 1·78 | 4·6 | 170/16 | 170/80 | 25/8 | 50 | 95 | 100 |
| 5 | 55 | 2·07 | 5·5 | 165/10 | 165/93 | 17/4 | 95 | 75 | 100 |
| 6 | 53 | 2·06 | 3·5 | 120/4 | 120/65 | 25/8 | 50 | 100 | 100 |
| 7 | 45 | 2·05 | 4·4 | 160/15 | 160/90 | 40/10 | 0 | 0 | 50 |
| 8 | 59 | 2·08 | 7·0 | 200/25 | 200/90 | 22/8 | 0 | 0 | 75 |

BSA, body surface area; LV, left ventricle; PA, pulmonary artery.

*The cardiac output was measured by the Fick method.

†The maximum percentage narrowings of the left anterior descending (LAD), left circumflex (LC), and right coronary arteries (RCA) are given.

## Patients and methods

Eight men with ischaemic heart disease were selected for the study. Their ages ranged from 45 to 65 (Table). All had had cardiac catheterization less than a week before the non-invasive study. All the patients had symmetrical left ventricular contraction without dyskinetic areas. The relevant haemodynamic and angiographic data are presented in the Table. All the patients had previously used nitroglycerin successfully for angina pectoris. None was on digitalis or beta-adrenergic blocking agents at the time of the study.

For the echographic study, a Unirad 100 Series Diagnostic Echoscope was used with a Tektronix 174 strip-chart recorder. Standard procedures (Feigenbaum, 1973) were used for the identification and recording of the left ventricular dimension and posterior wall thickness. Simultaneously, an electrocardiographic lead showing clearly the onset of the QRS complex, an indirect carotid displacement curve, and a phonocardiogram, were recorded at a paper speed of 75 mm $s^{-1}$ (Fig. 1). The phonotransducer was placed over the third intercostal space at the left sternal edge. The low cut-off phonofilter was set at 100 Hz. The following systolic time intervals (STI) were calculated as described by Weissler, Harris, and Schoenfeld (1968): total electromechanical systole (QA2), left ventricular

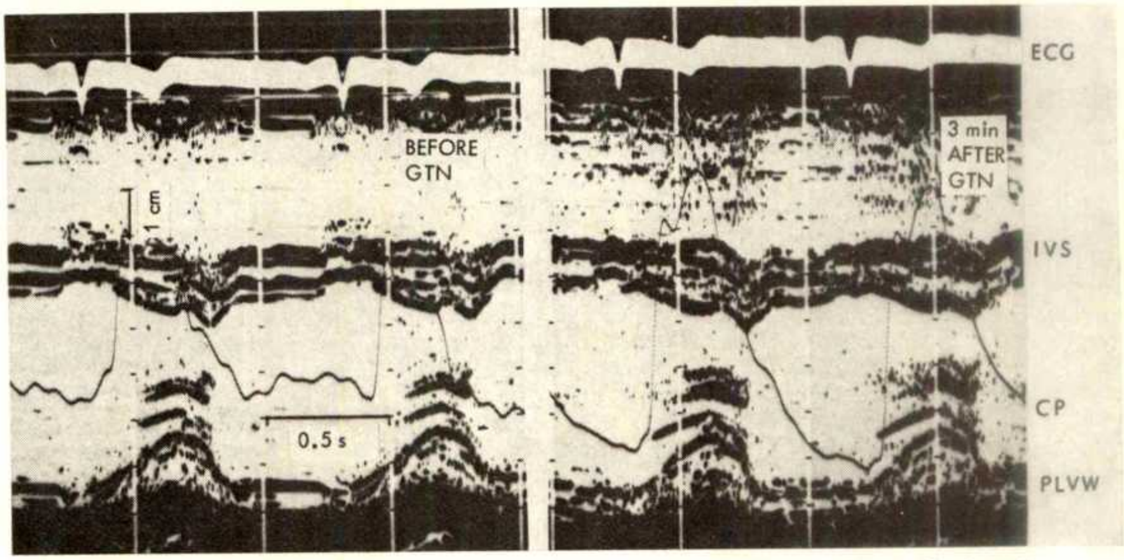

FIG. 1 *Echocardiographic recordings of left ventricular dimension before and after the administration of sublingual nitroglycerin (GTN). ECG, electrocardiogram; IVS, interventricular septum; CP, carotid pulse; PLVW, posterior left ventricular wall.*

ejection time (LVET), and pre-ejection period (PEP). All the intervals were measured to the nearest 5 ms and the means of at least 5 cardiac cycles calculated.

Three control recordings were obtained during normal respiration, with the patients tilted at 20 degrees from the horizontal. The arterial blood pressure was measured twice with a sphygmomanometer. One nitroglycerin tablet (0·6 mg) was given sublingually. Recordings were obtained at 10-second intervals for 5 minutes and the blood pressure was measured at 30 s intervals. Care was taken to keep the position of the echotransducer constant during the study. The left ventricular end-diastolic dimension was measured 40 ms after the onset of the QRS complex and the end-systolic dimension at the time of minimum distance between the two endocardial surfaces. All the patients had normal septal motion.

The mean velocity of circumferential fibre shortening ($V_{CF}$) was estimated as:

$$V_{CF} = \frac{LVDD - LVSD}{LVDD \times LVET} \text{ (circumferences s}^{-1}\text{)}$$

where LVDD and LVSD represent the left ventricular end-diastolic and end-systolic dimensions. The left ventricular volume, stroke volume, and cardiac output were calculated as described by Fortuin *et al.* (1971). The mean arterial blood pressure was calculated as the diastolic blood pressure plus one-third of the pulse pressure. The total peripheral resistance was obtained by dividing the mean arterial blood pressure by the echographically estimated cardiac output. The left ventricular wall stress ($\sigma$) was estimated during mid-ejection from the equation:

$$\sigma = \frac{1 + b^3/2r^3}{b^3 - a^3} Pa^3$$

where P is the left ventricular systolic blood pressure, 'a' the inner radius of the left ventricle, and 'b' the outer radius, i.e. 'a' plus posterior wall thickness. The geometrical shape of the ventricle was thus assumed to be a thick-walled sphere (Mirsky, 1974). Mid-ejection was timed at LVET/2 before the aortic closure sound. The wall stress was calculated for the midwall of the left ventricle, substituting $(a+b)/2$ for r.

Student's t-test was used for the comparison of paired data.

## Results

The results given are those for the control period and for 3 minutes after the administration of nitroglycerin, when the maximal changes in heart rate, arterial blood pressure, and left ventricular dimension occurred.

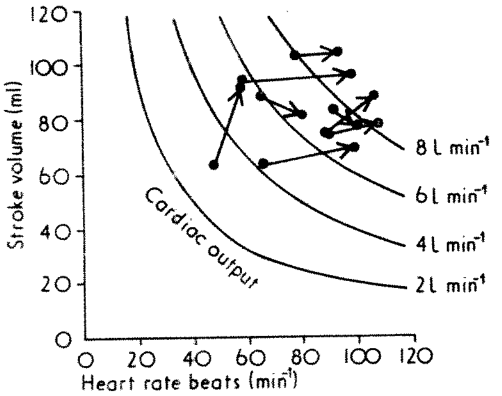

FIG. 2 *Changes in heart rate, stroke volume, and cardiac output, after nitroglycerin.*

The systolic blood pressure decreased from 142 ± 7 (SEM) mmHg in the control period to 116 ± 7 mmHg ($P < 0.001$) and the diastolic pressure from 84 ± 3 to 74 ± 2 mmHg ($P < 0.001$). The calculated mean blood pressure also decreased significantly, from 105 ± 4 to 88 ± 3 mmHg ($P < 0.001$). The end-diastolic and end-systolic dimensions of the left ventricle both decreased significantly, from 5·2 ± 0·2 cm to 4·9 ± 0·2 cm ($P < 0.05$), and from 4·2 ± 0·2 cm to 3·7 ± 0·2 cm ($P < 0.001$), respectively. Corresponding changes were seen in the calculated left ventricular end-diastolic and end-systolic volumes, from 155 ± 15 ml to 139 ± 13 ml ($P < 0.05$) and from 75 ± 10 to 53 ± 11 ($P < 0.001$), respectively. The end-diastolic posterior wall thickness did not change significantly after nitroglycerin. The cardiac output, as estimated from the left ventricular volumes and the heart rate, was increased from 5·8 ± 0·6 l min$^{-1}$ to 7·7 ± 0·6 l min$^{-1}$ ($P < 0.001$). However, with one exception, this was the result of an increase in heart rate from 72 ± 5 to 90 ± 6 beats per minute ($P < 0.001$), while the stroke volume did not change significantly from the resting value of 80 ml (Fig. 2). The total peripheral resistance, however, decreased from 18 ± 4 to 11 ± 1 units ($P < 0.001$).

The ejection fraction increased after nitroglycerin administration from 53 ± 3 per cent to 65 ± 6 per cent ($P < 0.001$) and the $V_{CF}$ increased from 0·81 ± 0·05 to 1·15 ± 0·10 circ s$^{-1}$ ($P < 0.001$). The calculated midsystolic midwall stress decreased from 155 ± 14 to 102 ± 11 g cm$^{-2}$ ($P < 0.001$). No significant changes were seen in the rate corrected systolic time intervals: LVETI was 400 ± 9 before and 390 ± 6 at 3 minutes after nitroglycerin; PEPI was 141 ±3 and 143 ±3 and QA2I was 542 ±8 and 531 ±6 before and after nitroglycerin.

## Discussion

Recently, interest has been growing in the use of agents which decrease left ventricular afterload for the treatment of patients with myocardial infarction (Franciosa *et al.,* 1974; Hirshfeld *et al.,* 1974) or contraction abnormalities in chronic ischaemic heart disease (Helfant *et al.,* 1974; Dove, Shah, and Schreiner, 1974). In the present study, echocardiographic techniques were used for the estimation of afterload as expressed by the left ventricular wall stress, before and after the administration of nitroglycerin. These changes in afterload can be related to the attendant variations in $V_{CF}$ (Fig. 3). Since the long axis of the left ventricle cannot be measured echocardiographically, a thick-wall spherical model is assumed, and the formula used allows estimations of wall stress to be made at any given level through the wall thickness. This model can, however, only be applied to symmetrically contracting ventricles. Ratshin, Rackley, and Russell (1974) have shown that when left ventricular wall stress is calculated, using intracavitary pressure recordings with measurements of left ventricular dimension by echocardiography and by simultaneous angiography, similar results are obtained by both techniques. When intracardiac pressure recordings are not available, only the peak systolic blood pressure, measured sphygmomanometrically, can be used. The peak systolic pressure is assumed to occur at mid-ejection and the left ventricular dimension can be estimated at this moment as described above.

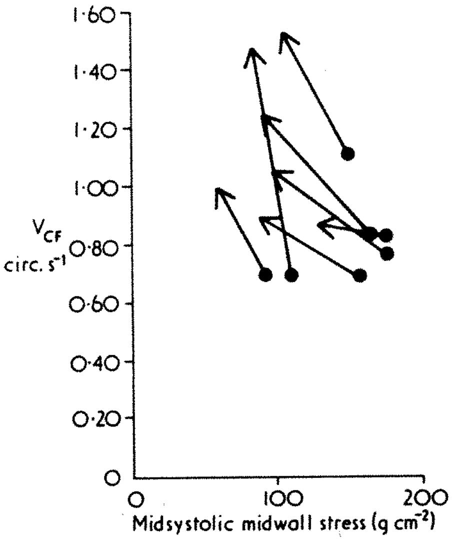

FIG. 3 *Changes in the velocity of circumferential fibre shortening ($V_{CF}$) and midsystolic midwall stress after nitroglycerin.*

Although the peak left ventricular wall stress usually occurs early in systole, the wall stress at mid-ejection is probably comparable in any individual patient before and after acute interventions. If the wall stress falls nearly linearly from an early systolic peak (Mirsky, 1968), the midsystolic measurement can be used as an approximate measure of the mean systolic stress and therefore correlated with the mean velocity of circumferential fibre shortening.

In spite of the usually reported good correlations between echocardiographic and angiocardiographic left ventricular dimensions, there is considerable scatter at all levels (Fortuin *et al.,* 1971; Gibson, 1973). The wide confidence margins are reflected in the absolute values for wall stress. However, recent studies (Redwood *et al.,* 1974) have supported the use of echocardiographic left ventricular dimensions in the study of the effects of haemodynamic interventions. In the present context, directional changes in wall stress are emphasized.

Fig. 3 shows that in all the patients, a decrease in left ventricular afterload was accompanied by an increase in $V_{CF}$, thus illustrating a modified force-velocity relation. With decreased afterload and total peripheral resistance, the increased $V_{CF}$ cannot be attributed to increased left ventricular contractility, even though the left ventricular end-diastolic volume was decreased. Isolated muscle studies (Zelis *et al.,* 1970a, b) have failed to show any alteration in contractility after moderate doses of nitroglycerin. However, in man, nitroglycerin may elicit reflex sympathetic activity as a result of its vasodilator action (Zelis *et al.,* 1970a, b). In a recent study, DeMaria *et al.* (1974), reported a small decrease in $V_{CF}$ after nitroglycerin. In that study, however, left ventricular ejection time was measured from the beginning of the QRS complex to the time of maximal anterior position of the posterior left ventricular wall, assuming a pre-ejection period of 50 ms. This method is probably less reliable than that using the indirect carotid tracing; the implied prolongation of left ventricular ejection time after nitroglycerin is also at variance with results of this and previous studies (Sawayama *et al.,* 1973). Redwood *et al.* (1974) found an increase in $V_{CF}$ from 1·3 to 1·7 circ $s^{-1}$ in their normal subjects, a change similar to that observed in our patients. The increase in cardiac output found in the present study exceeds the insignificant increases observed by DeMaria *et al.* (1974), and Burggraf and Parker

(1974). The changes in cardiac output are probably largely determined by the relative predominance of venous or arteriolar dilatation (Mason and Braunwald, 1965). A dominant arteriolar depressant effect is likely in our group of patients.

Opinion is still divided as to whether nitroglycerin relieves angina pectoris mainly by its effect on left ventricular pump function or by coronary vasodilatation (Cohn and Gorlin, 1974). In 1867, Brunton reported after Gamgee that amyl nitrite 'greatly lessens the arterial tension both in animals and man . . . which led me to try it in angina pectoris'. The present study confirms earlier reports (Brachfeld, Bozer, and Gorlin, 1959; DeMaria *et al.*, 1974; Burggraf and Parker, 1974) that arterial pressure and left ventricular dimensions are decreased after nitroglycerin, both effects combining to produce a sharp decrease in afterload or wall stress. Preload, as reflected by the left ventricular end-diastolic dimension, is also significantly reduced. Directional changes in myocardial oxygen consumption cannot be predicted from these data, since its main determinants are changed in opposite directions. It is likely, nevertheless, that the abrupt fall in wall tension would override changes having a contrary effect, producing a net decrease in myocardial oxygen requirements. This effect alone, regardless of possible increases in coronary blood flow, might successfully relieve angina pectoris in many patients. However, there is some evidence (Kjekshus, 1973) that a reduction of left ventricular preload may by itself improve coronary blood flow to underperfused subendocardial areas. Both the postulated mechanisms of action of nitroglycerin may, therefore, be operating.

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# Angiographic abnormalities associated with alterations in regional myocardial blood flow in coronary artery disease[1, 2]

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*To evaluate the association between alterations in myocardial blood flow and angiographic findings, myocardial blood flow was compared in 26 patients with asynergy, 15 patients with a similar extent of coronary artery disease but without asynergy, and 10 patients without coronary artery disease or obvious myocardial or valvular disease. Myocardial blood flow was measured at rest with an Anger camera and PDP-11/20 computer after the intracoronary injection of* $^{133}$*xenon. In comparison with the normal subjects, whole heart blood flow was significantly reduced in patients with asynergy. In addition, myocardial blood flow in regions of anteroapical asynergy was reduced (85·7 ± 7·0 ml/min per 100 g*[3] *in controls to 65·4 ± 4·5,* $P<0·05$*) and a similar reduction was noted in regions of posterolateral asynergy (91·5 ± 8·8 in controls to 66·8 ± 5·0,* $P<0·05$*). In general, regional myocardial blood flow was reduced distal to left anterior descending or left circumflex stenosis of >50 per cent, with a trend toward further reduction distal to >75 per cent stenosis. In these same patients, the presence of anteroapical or posterolateral asynergy resulted in a similar trend to even greater reduction of flow. The effect of collaterals was variable: 7 of 8 patients without asynergy but with >75 per cent left anterior descending stenosis and collateral circulation to the lower left anterior descending quadrant had minimally reduced flows. However, in the 17 patients with anteroapical asynergy, regional myocardial blood flow was very similar in the 9 patients with collaterals compared with the 8 patients without them. This study suggests that the degree of coronary artery stenosis and presence of asynergy are both important in evaluating alterations in myocardial blood flow in coronary artery disease, while the role of collaterals remains uncertain.*

The relation between alterations in regional myocardial blood flow and angiographic abnormalities of the coronary arteries and left ventricle remains unclear (Cannon, Dell, and Dwyer, 1972a; Klocke *et al.*, 1974). In the present study, we have approached this problem by measuring whole heart blood flow and regional myocardial blood flow simultaneously, and by noting (1) to what extent regional flow is reduced in areas of abnormal left ventricular wall motion (asynergy) and (2) what the relation of this flow reduction is to the degree of asynergy, the degree of coronary artery stenosis, and the presence or absence of coronary collateral circulation.

## Patients and methods

### Patient selection

After giving informed consent, 51 patients with a chest pain syndrome were evaluated with biplane left ventriculography and selective coronary angiography, followed by selective injection of $^{133}$xenon into the left main coronary artery. These patients were not selected in any systematic fashion except that patients with unstable angina or concomitant cardiomyopathies or valvular heart disease were excluded. This series included 10 patients with a chest pain syndrome and normal coronary arterio-

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[3] Mean ± SEM.

grams and left ventriculograms. This normal control group of 7 men and 3 women did not have any clinical or angiographic evidence of valvular disease or primary myocardial disease. The mean age of this group was 46 years (range 38 to 57).

## Catheterization procedure

Each patient was in the fasting state and was premedicated with 50 mg diphenhydramine and 10 mg diazepam orally or intramuscularly. Right and left heart catheterization with biplane left ventriculography were performed. Selective coronary angiography was then done via the femoral approach, followed by blood flow measurements using $^{133}$xenon.

All data concerning percentage luminal diameter stenosis and presence or absence of collaterals were determined by the consensus of 3 independent investigators. Axis shortening from end-diastole to end-systole was determined from hand-drawn ventriculographic silhouettes. End-diastole was defined as the largest silhouette, end-systole the smallest. One investigator drew all silhouettes to ensure standardization of technique and to eliminate possible intraobserver differences (Cohn *et al.*, 1974b). Only the first 4 regularly conducted beats after complete opacification of the ventricle were used. The reproducibility of these silhouettes from one early beat to the next in the same ventriculogram has been previously shown in our laboratory (Cohn *et al.*, 1974b). The lower limits of normal values for axis shortening in our laboratory are $\geqslant 10$ per cent shortening in the longitudinal axis in the right anterior oblique projection and $\geqslant 20$ per cent shortening in the major transverse axes in both the right and left anterior oblique projections. Posterolateral asynergy was evaluated in the left anterior oblique projection (Cohn *et al.*, 1974a). Posterolateral hypokinesis was defined as 5 to 20 per cent shortening in the posterolateral transverse radius in this projection and akinesis as $<5$ per cent shortening in this radius. Posterolateral dyskinesis was not observed in this series of patients. Anteroapical hypokinesis was defined as either 2 to 10 per cent shortening in the longitudinal axis in the right anterior oblique projection and/or 5 to 20 per cent shortening in the anterior transverse radius; akinesis was defined as $<2$ per cent shortening in the longitudinal axis and $<5$ per cent shortening in the transverse radius. Again, anteroapical dyskinesis was not present in this series of patients. No attempt was made to evaluate septal asynergy in the left anterior oblique projection because of variable effects on septal motion depending on the level of obstruction in the left anterior descending artery, and because flow in the right coronary artery—which usually supplies the posterior part of the septum—was not studied. Patients with both posterolateral and anteroapical asynergy were assigned to one of the two respective subgroups depending on which was the more severe abnormality.

At least 10 minutes were allowed to elapse between the last injection of contrast medium (meglumine and sodium diatrizoate) for diagnostic coronary angiography before the selective injection of xenon was attempted. To allow haemodynamic values to return to baseline levels, at least 30 minutes were allowed to elapse between the last sublingual administration of nitroglycerin and the intracoronary injection of xenon.

## Measurement of regional myocardial blood flow

The patient was placed in the left anterior oblique position under the fluoroscopy unit where the centre and borders of the heart were marked on the chest. The table was then placed under the Anger scintillation camera (Nuclear Chicago Pho/Gamma HP). A radioactive source was moved over the borders of the heart, and the relation between the camera detector and the table was recorded. The patient was repositioned under the fluoroscopy unit, a catheter was placed in the left main coronary artery and its position confirmed by injection of 0·25 ml contrast material. The table was repositioned under the Anger camera in the left anterior oblique position, and 20 to 25 mCi of $^{133}$Xe in 2 ml saline were injected followed by a 3 ml saline flush. The catheter was then removed from the coronary artery.

Washout curves were constructed using 2-second time frames from the peak to 40 seconds afterwards, and regional washout curves were obtained by placing electronic cursors over the proximal and distal portions of the left anterior descending and left circumflex coronary arteries (4 quadrants) (Fig. 1). The position of these vessels was determined from the initial frames of the gamma camera image during the arterial phase of the study and myocardial blood flow was calculated from the initial slope of the xenon clearance curve (Ross *et al.*, 1964; Cannon, Dell, and Dwyer, 1972b; Holman *et al.*, 1974). To minimize possible effects of fat or other non-muscular components of myocardium on the blood flow calculation, only the slope of the curve representing the first 40 seconds of washout data was computed using a non-weighted monoexponential least squares programme, and the standard deviation of the slope was calculated. From the initial slope, an index of myocardial blood

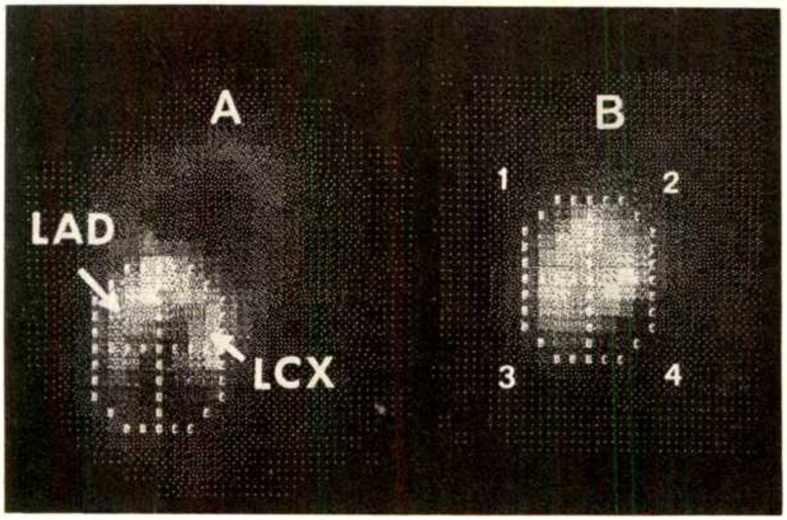

FIG. 1 *Using the left anterior oblique projection, the distribution of perfusion in the left coronary artery was determined in the first 5 seconds after the xenon injection. During this phase (A), xenon was primarily intravascular, thus delineating the major branches of the left anterior descending (LAD) and left circumflex (LCX) arteries. Electronic cursors were then placed over the proximal and distal portions of these vessels. (B) Once the xenon had been distributed throughout the myocardium, 4 regions were defined, representing tissue perfused by the proximal LAD (1), proximal LCX (2), distal LAD (3), and distal LCX (4). Regional clearance curves were then obtained from each quadrant.*

flow in ml/min per 100 g was determined, using the equation

$$F/W = \frac{100\,k\lambda}{\rho}$$

where k was the mean slope calculated from 0 to 40 seconds, $\lambda$ was the blood/tissue partition coefficient (assumed to be 0·72), and $\rho$ was the specific gravity (assumed to be 1·05). During our initial investigation of the accuracy and sensitivity of this technique (Holman *et al.*, 1974), 3 patients underwent reproducibility studies comparing the initial slopes of xenon washout; the mean difference in quadrant blood flow between the two runs was 3·0 ml/min per 100 g (3·8%) and the standard deviation was 3·2 ml/min per 100 g (4·0%). The correlation coefficient for quadrantic flows from run 1 compared with run 2 was 0·971.

### Relating regional myocardial blood flow to areas of left ventricular myocardium on the ventriculogram

Blood flow values were determined in the left anterior oblique projection (Fig. 1). Using the same spacial orientation, the left anterior oblique coronary angiogram was superimposed upon the left anterior oblique gamma camera image of the left ventricle. As a result, quadrant No. 3 represented myocardium perfused by the left anterior descending and quadrant No. 4 represented myocardium perfused by the left circumflex. Thus, the flow distal to a stenosed left anterior descending or left circumflex could be evaluated. Next, the site of asynergy (when present) was compared with the respective quadrantic myocardial blood flow values. (Analysis of asynergy corresponding to upper left anterior descending and upper left circumflex quadrants was not attempted because regions of myocardium both proximal and distal to a stenosis may overlap one another.) Evaluation of the angiograms was performed without prior knowledge of the quadrantic flow measurements, and vice versa.

## Results

### Whole heart blood flow and asynergy

Fifteen patients (13 men and 2 women) had coronary artery disease and no asynergy. Their mean age was 48 years (range 36 to 52). Twenty-six patients (22 men and 4 women) with coronary artery disease had asynergy. Their mean age was 48 years (range 36 to 61). Seventeen had predominant antero-

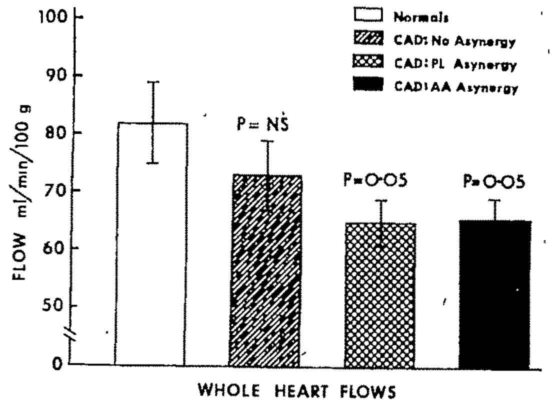

FIG. 2 *Whole heart flows (mean ± SEM) in 10 normal controls compared with 15 patients with coronary artery disease (CAD) and no asynergy, 17 patients with predominant posterolateral (PL) asynergy, and 9 patients with predominant anteroapical (AA) asynergy.*

apical asynergy, and 9 had predominant posterolateral asynergy. Whole heart flow in the normal group (mean ± standard error = 82·1 ± 7·1 ml/min per 100 g) was greater than any of the coronary artery disease groups. In Fig. 2, a trend in reduction of mean flow is shown from normal controls to coronary artery disease patients without asynergy (72·9 ± 6·1)[1] and finally to coronary artery disease patients with anteroapical (65·3 ± 3·9, P = 0·05) or posterolateral asynergy (64·7 ± 3·8, P = 0·05).

## Regional myocardial blood flow in areas of asynergy

**Posterolateral asynergy** In the lower left circumflex quadrant, a trend in reduction of flow from normal controls (91·5 ± 8·8) to patients with coronary artery disease without posterolateral asynergy (75·0 ± 4·8), and finally to patients with coronary artery disease and posterolateral asynergy (66·8 ± 5·0, P < 0·05) was also noted (Fig. 3).

**Anteroapical asynergy** Similarly, in the lower left anterior descending quadrant, a trend in reduction of flow was again observed from normal controls (85·7 ± 7·0), to patients with coronary artery disease without anteroapical asynergy (74·9 ± 5·2) and to patients with coronary artery disease and anteroapical asynergy (65·4 ± 4·5, P < 0·05) (Fig. 3).

## Regional myocardial blood flow in areas of akinesia compared with areas of hypokinesia

**Posterolateral asynergy** Of the 9 patients with posterolateral asynergy, 3 had akinesia and 6 had hypokinesia. Lower left circumflex quadrant flow in the 3 patients with akinesia was 53·3 ± 6·3, while the 6 with hypokinesia had higher mean flows (73·5 ± 5·9, P < 0·05).

**Anteroapical asynergy** In the 17 patients with anteroapical asynergy, 7 had akinesia and 10 had hypokinesia. Unlike the lower left circumflex quadrant, mean lower left anterior descending quadrant flows with respect to akinesia or hypokinesia were similar.

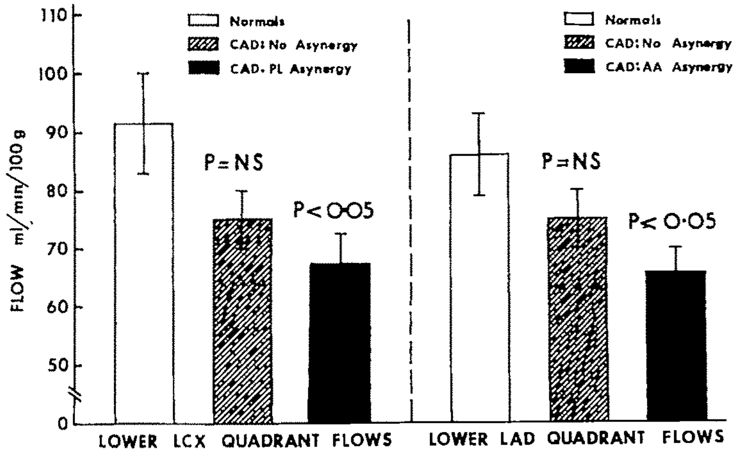

FIG. 3 *The same format as in Fig. 2, only now* regional *myocardial blood flow (mean ± SEM) in the lower left circumflex (LCX) and anterior descending (LAD) quadrants in normal controls are compared with patients with coronary artery disease (CAD) and no asynergy, and either posterolateral (PL) or anteroapical (AA) asynergy.*

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[1] Only significant P values will be noted in remainder of text.

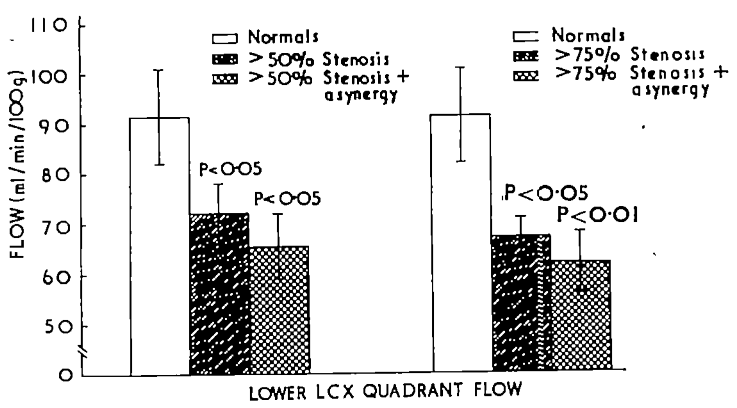

FIG. 4 *Relation between regional myocardial blood flow (mean ±SEM), degree of left circumflex (LCX) stenosis, and posterolateral asynergy. P values compared with 10 normal controls. 27 patients had >50 per cent stenosis and 7 of the 27 had asynergy. 14 patients had >75 per cent stenosis and 5 of the 14 had asynergy.*

### Relation between regional myocardial blood flow, degree of coronary artery stenosis, and presence of asynergy

**(A) Degree of vessel stenosis considered separately** *Left circumflex* Regional myocardial blood flow in the lower left circumflex quadrant distal to a left circumflex stenosis of >50 per cent in 27 patients is depicted in Fig. 4 (14 of these 27 patients had >75 per cent stenosis of left circumflex). There was a trend in reduction of mean flows from normal controls (91·5 ±8·8) to all patients with >50 per cent stenosis (71·7 ±3·8, P<0·05) to only those patients with >75 per cent left circumflex stenosis (66·7 ±4·1, P<0·01).

*Left anterior descending* Regional myocardial blood flow in the lower left anterior descending quadrant distal to a left anterior descending stenosis of >50 per cent in 39 patients is depicted in Fig. 5 (19 of these 39 patients had >75 per cent stenosis of left anterior descending). There was again a trend in reduction of mean flows from normal controls (85·7 ±7·0) to all patients with >50 per cent stenosis (70·5 ±3·5) to only those patients with >75 per cent left anterior descending stenosis (68·2 ±4·1, P<0·05).

**(B) Degree of coronary artery stenosis and asynergy** *Left circumflex stenosis with posterolateral asynergy* Seven of the 9 patients with posterolateral asynergy had >50 per cent stenosis of left circumflex (5 had >75% stenosis) and all patients in this group had >75 per cent stenosis of the right coronary artery. Since the right coronary artery was >75 per cent stenosed in all patients in this group, the influence of degree of left circumflex stenosis on

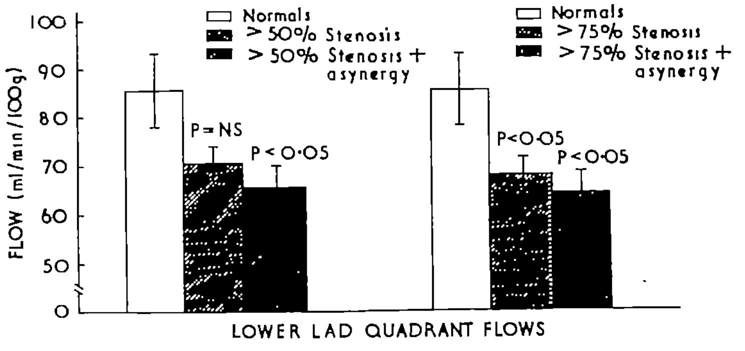

FIG. 5 *Relation between regional myocardial blood flow (mean ±SEM), degree of left anterior descending (LAD) stenosis, and anteroapical asynergy. P values compared with 10 normal controls. 39 patients had >50 per cent stenosis and 17 of the 39 had asynergy. 19 patients had >75 per cent stenosis and 11 of the 19 had asynergy.*

asynergy could not be reliably determined as both the right coronary artery and left circumflex may nourish the lower left circumflex quadrant in any one patient (See, Giddings, and Cosby, 1974). However, with >50 per cent left circumflex stenosis, the presence of posterolateral asynergy was associated with a trend toward lower left circumflex quadrant flow (71·7 ±3·8 to 65·4 ±6·0) (Fig. 4). With both >75 per cent left circumflex stenosis and posterolateral asynergy, this trend was again seen (66·7 ±4·1 to 61·7 ±6·5). In the remaining 2 patients with <50 per cent left circumflex stenosis and asynergy, the right coronary artery was stenosed >75 per cent and it could not be determined which vessel influenced the presence of posterolateral asynergy.

*Left circumflex stenosis without posterolateral asynergy* Twenty patients had >50 per cent left circumflex stenosis without posterolateral asynergy. Flow in these patients was greater (but not significantly) compared with patients with asynergy. In the absence of flow measurements in the right coronary artery, these values may be misleading, as we have commented earlier.

*Left anterior descending stenosis with anteroapical asynergy* All 17 patients with anteroapical asynergy had >50 per cent stenosis of the left anterior descending artery; 11 of these 17 patients had >75 per cent stenosis of the left anterior descending artery, with mean flow in the lower left anterior descending quadrant of 64·1 ±4·5, $P < 0·05$ (Fig. 5). With >50 per cent left anterior descending stenosis, the presence of anteroapical asynergy was associated with a trend in reduction of lower left anterior descending quadrant flow (70·5 ±3·5 to 65·4 ±4·5). In addition, with both >75 per cent left anterior descending stenosis and anteroapical asynergy, this trend was again present (68·2 ±4·1 to 64 ±4·5).

*Left anterior descending stenosis without anteroapical asynergy* Twenty-two patients had >50 per cent stenosis of the left anterior descending artery and no anteroapical asynergy with lower left anterior descending quadrant mean flow greater (but not significantly) compared with patients with asynergy. Eight of the 22 patients without asynergy had >75 per cent left anterior descending stenosis and no anteroapical asynergy, and mean flow to the lower left anterior descending quadrant was very similar to that of patients with >50 per cent left anterior descending stenosis.

### Relation between regional myocardial blood flow, asynergy, and collateral circulation

**Left circumflex** All 9 patients with posterolateral asynergy had angiographically apparent collaterals to the lower left circumflex quadrant. Thus, the influence of the absence of collaterals on flow to areas of posterolateral asynergy could not be surmised. The relative influence of collaterals on flow also could not be determined in the lower left circumflex quadrant because collaterals to the right coronary artery or left circumflex or both could be recorded as flow to this quadrant in the same patient (Cosby, Giddings, and See, 1974).

**Left anterior descending** In the 17 patients with anteroapical asynergy, 9 had angiographically apparent collaterals to the lower left anterior decending quadrant, while 8 did not, and mean flows were very similar. Greater than 75 per cent stenosis was present in all cases with collaterals and only 3 patients with >75 per cent stenosis and asynergy did not have collaterals. All 3 had greatly reduced flow (<45 ml/min per 100 g). Eight patients had >75 per cent left anterior descending stenosis without anteroapical asynergy. In these 8 patients, 7 had angiographically apparent collateral flow to the lower left anterior descending quadrant with mean flows of 77·6 ±7·6.

## Discussion

Ross *et al.* (1964), using $^{133}$Xe, reported no difference in whole heart blood flow in patients with or without coronary artery disease. Though they studied 4 patients with left coronary artery disease, they did not specify the degree of stenosis. More recently, Klocke *et al.* (1974), in reviewing the question of whether there is a reduction of whole heart coronary blood flow per unit mass of left ventricle in patients with coronary artery disease, concluded that average myocardial blood flow was significantly decreased at rest when helium was used as a tracer. They suggested that similar correlations with $^{133}$Xe clearance techniques might result (despite the methodological limitations of this technique) if *regional* reductions in flow could be related to localized arteriographic abnormalities. Using $^{133}$Xe in that manner, Cannon *et al.* (1972a) noted a significant decrease in myocardial blood flow distal to a >75 per cent stenosed coronary artery. Dwyer, Dell, and Cannon (1973), studying regional myocardial blood flow with the same technique in patients with prior transmural infarctions, noted significantly decreased myocardial blood flow in areas of the anterior left ventricle distal to a >80 per cent stenosed left anterior descending coronary artery and of the right ventricle distal to a >80 per cent stenosed right coronary artery. (They also noted that the right coronary artery appeared to contribute very little flow to the inferior left ventricle in humans.) In the present series of patients, we studied regional myocardial blood flow in areas of left ventricular asynergy in 26 patients with coronary artery disease via injections of $^{133}$Xe into the left coronary artery irrespective of prior clinical or electrocardiographic evidence of myocardial infarction. Ten controls with normal coronary arteries and 15 patients with coronary artery disease and no asynergy were also studied for purposes of comparison.

The effects of both extent of vessel disease and of left ventricular dysfunction (especially asynergy) on mortality have been reported by several groups (Oberman *et al.,* 1972; Bruschke, Proudfit, and Sones, 1973a, b; Nelson, Cohn, and Gorlin, 1975; Moraski *et al.,* 1975) and are of great prognostic importance. Our data indicate that whole heart blood flow is significantly reduced, compared with control subjects, only in coronary artery disease patients with asynergy (Fig. 2). Similarly, *regional* myocardial flow in the lower left anterior descending or left circumflex quadrants was also significantly reduced compared with control subjects only in patients with either anteroapical or posterolateral asynergy, respectively (Fig. 3). In patients with coronary artery disease but no asynergy, we observed whole heart and regional myocardial blood flow to be intermediate between normal controls and patients with asynergy. A trend was shown in which patients with >75 per cent stenosis had the greatest reduction in flow, especially when asynergy was also present (Fig. 4 and 5). Though our data do not indicate that akinesis is associated with lower flows than hypokinesis, this is not totally unexpected, since the ventriculographic finding of akinesis may not always be a precise indicator of fibrosis, i.e. non-scarred regions that are temporarily ischaemic may appear akinetic (Dyke *et al.,* 1974). Therefore, reduced flow in some patients with coronary artery disease may be the primary cause of asynergy because of ischaemia, while in others it may be the secondary result of reduced myocardial oxygen requirements in an area of scarred left ventricle. The role of collateral vessels is also not clear from the present data, despite the finding that regional myocardial flow was very low in patients with asynergy but without collaterals.

Our study indicates that the evaluation of myocardial blood flow in patients with coronary artery disease should take into account the presence of asynergy as well as the degree of vessel stenosis and presence of collateral vessels. First, there are difficulties in evaluating the degree of stenosis of a coronary artery, which have been related to variation from observer to observer (Björk *et al.,* 1975), as well as the finding that postmortem evaluation of stenosis and angiographic evaluation may be at variance (Vlodaver *et al.,* 1973). Second, vessels may at one time have been more severely stenosed with subsequent recanalization (Chandler, 1972). These two observations may explain the similar flow data in patients with >50 per cent stenosis compared with >75 per cent stenosis. On the other hand, asynergy alone may be an unreliable indicator of reduced flow since asynergic regions may consist of islands of viable tissue interspersed within a sea of fibrosis or vice versa (Schwartz and Mitchell, 1962). In addition, collateral circulation may possibly alter flows in areas of asynergy (Banka, Bodenheimer, and Helfant, 1974), and asynergy in the absence of coronary artery disease (as in primary myocardial disease) may be associated with normal or high coronary blood flow (Horwitz *et al.,* 1974). Thus, while the present study confirms the advantages of measuring regional myocardial blood flow, rather than only whole heart blood flow, it also suggests the need to relate flow data to the results of two-state left ventriculography (Cohn and Gorlin, 1975) to determine total and regional contractile reserve. There is also a need for further regional myocardial blood flow measurements in a second state in which either the heart is metabolically stressed or maximal hyperaemia is induced (Gould *et al.,* 1974). These additional data will help to clarify the role of collateral vessels as well as assessing the haemodynamic significance of coronary artery lesions on the arteriogram.

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# Longitudinal study of heart size in older people

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*Transverse cardiac diameter and transverse thoracic diameter were measured in a longitudinal study of older men and women at the original examination and after five years. The cardiothoracic ratio overestimated 5-year changes in heart size, because of significant decreases with age in transverse thoracic diameter. A regression equation to predict transverse cardiac diameter from age and weight had been previously computed from the data obtained at the initial examination. This was a satisfactory predictor of recorded 5-year changes except in women of 70 years and over at entry to the study in whom the predicted change was significantly larger than the recorded change. This had resulted from the death during the 5 years of women in that age group with larger transverse cardiac diameters.*

A previous paper described measurements of transverse cardiac diameter and transverse chest diameter in a random sample of older people (Milne and Lauder, 1974). The conclusion drawn from analysis of these cross-sectional data was that the cardiothoracic ratio was an unsatisfactory estimate of heart size in the elderly because of decrease in the transverse chest diameter as age increased. Transverse cardiac diameter was a better estimate of heart size, and equations were derived to predict this diameter from age and weight. In both sexes, the transverse cardiac diameter increased significantly as age increased.

The present paper describes the result of remeasurement of the survivors of the original study after 5 years. A comparison has also been made of cross-sectional with longitudinal data.

## Methods

The original study was made on 215 men and 272 women aged 62 to 90 years who formed a simple random sample from 27 000 older people living in a defined area of Edinburgh. The method of sampling has been fully described elsewhere (Milne, Maule, and Williamson, 1971). The persons examined in the present study were those members of the original sample who were alive after 5 years and who were willing to attend for re-examination. These numbered 113 men and 148 women. The follow-up of persons in the sample has been fully described elsewhere (Milne and Chopin, 1975).

Posteroanterior chest $x$-rays were taken at both examinations, at a tube-film distance of 183 cm (6 ft) at the height of a less than maximal inspiration. The transverse cardiac diameter and the transverse chest diameter were measured to the nearest millimetre on the films, using a Harpenden anthropometer (Tanner and Whitehouse, 1957) with straight branches. This sliding caliper allowed measurement of the transverse cardiac diameter in one simple operation (Milne and Lauder, 1974). The transverse chest diameter was measured from the internal surfaces of the ribs, superior to the costal attachment of the diaphragm, at the point where the chest width was greatest (Cowan, 1959). Suitable measurements of cardiac diameter were obtained in 113 men and 139 women and of chest diameter in 95 men and 137 women. The cardiothoracic ratio was expressed as 100 × (transverse cardiac diameter/transverse chest diameter). In the original sample the mean cardiac diameter was significantly larger in persons with diastolic pressures of 100 mmHg or more. This was no longer true in the 5-year examination and measurements of persons with these pressures (5 men, 18 women) were not excluded from the analysis. Unpublished data from the study show that the mean diastolic blood pressure in survivors after 5 years is significantly lower than at the original examination.

Reproducibility of the measurements was satisfactory. The method of testing this has been fully described elsewhere (Milne and Lauder, 1974).

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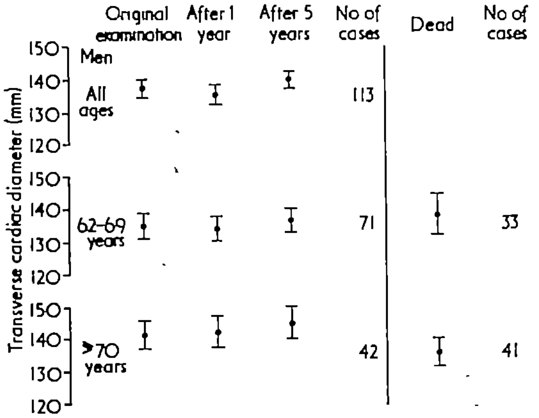

FIG. 1. *Mean transverse cardiac diameters with 95 per cent confidence limits in surviving men in a longitudinal study, and in those who died.*

## Results

Mean values of transverse cardiac diameter with 95 per cent confidence limits are given for men in Fig. 1 and for women in Fig. 2. Apart from the dead all measurements refer to those survivors who were examined after 5 years and ages given are on entry to the study. The age categories were 'below 70 years' and '70 years and over'.

The mean values suggested an increase in cardiac diameter over the 5-year period, but this did not reach statistical significance. In the men and younger women who died, cardiac diameters at the original examination did not differ from those in survivors. In women who died and who were 70 years and over on entry to the study, the mean cardiac diameter was significantly greater at the original examination than in surviving women of the same age group, both at the original examination and when measured again five years later.

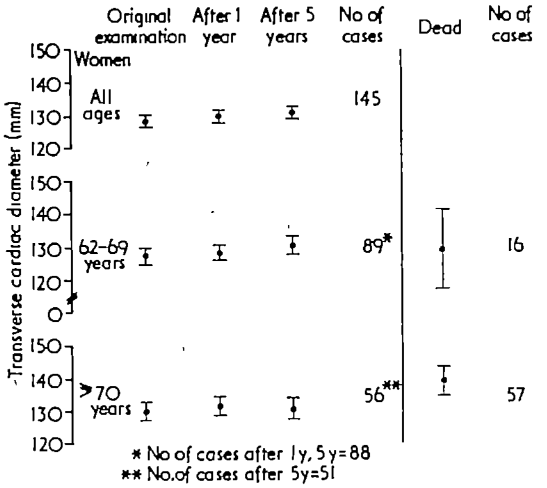

FIG. 2. *Mean transverse cardiac diameters with 95 per cent confidence limits in surviving women in a longitudinal study, and in those who died.*

Mean values and 95 per cent confidence limits of transverse chest diameter were similarly examined. No significant difference was found, when comparing appropriate age groups, among surviving or dead subjects. These values are, therefore, not reported further.

In each surviving subject the measurement of transverse cardiac diameter at the original examination was subtracted from the measurement at the 5-year examination. This was done also for the transverse chest diameter and for the cardiothoracic ratio. Mean differences with standard errors of these three variables are given in Table 1. Student's two-tail t test was used to test whether mean differences differed significantly from zero.

The tests showed that the mean differences in the cardiac diameter in 5 years were significant in men of 70 years and over (P < 0·05) and in women of 62 to 69 years (P < 0·001). The ages are those

TABLE 1 *Mean differences in transverse cardiac diameter, transverse chest diameter, and cardiothoracic ratio, after 5 years, in two age groups of older men and women*

| *Age (at entry)* | *Cardiac diameter (mm)* | | | *Chest diameter (mm)* | | | *Cardiothoracic ratio (%)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Mean difference* | *SE* | *No. of cases* | *Mean difference* | *SE* | *No. of cases* | *Mean difference* | *SE* | *No. of cases* |
| *Men* | | | | | | | | | |
| 62 to 69 y | 1·282 | 1·035 | 71 | –2 421* | 1 161 | 57 | 1·137* | 0·436 | 57 |
| ≥70 y | 3·643* | 1·509 | 42 | –1·237 | 2·184 | 38 | 1·253* | 0 552 | 38 |
| *Women* | | | | | | | | | |
| 62 to 69 y | 3·483*** | 0·793 | 88 | –2·553* | 1·108 | 85 | 1 939*** | 0·407 | 85 |
| ≥70 y | 1·784 | 1·228 | 51 | –3·462** | 1·194 | 52 | 1·439*** | 0 461 | 51 |

*P < 0·05 **P < 0·01 ***P < 0·001.

TABLE 2 *Regressions of transverse cardiac diameter on age and body weight in various groups of older men and women*

| *Sex and age* | *Group examined and time of examination* | *Intercept* | *Regression coefficient (age)* | *Regression coefficient (weight)* | *R* | *No. of cases* |
|---|---|---|---|---|---|---|
| *Men* | | | | | | |
| 62 to 90 y | All men at original examination | 61·762 | 0·413 | 0·692 | 0·62 | 188* |
| | 5-year survivors at original examination | 58·581 | 0·372 | 0·762 | 0·65 | 113 |
| | Dead (after 5 years) at original examination | 57·346 | 0·485 | 0·719 | 0·57 | 74 |
| | 5-year survivors at 5-year examination | 47·781 | 0·699 | 0·643 | 0·57 | 113 |
| *Women* | | | | | | |
| 62 to 90 y | All women at original examination | 42·942 | 0·646 | 0·661 | 0·61 | 201* |
| | 5-year survivors at original examination | 70·003 | 0·334 | 0·567 | 0·57 | 145 |
| | Dead (after 5 years) at original examination | 20·876 | 0·930 | 0·766 | 0·64 | 52 |
| | 5-year survivors at 5-year examination | 94·339 | 0·111 | 0·481 | 0·44 | 139 |

*Excludes persons with diastolic BP ≥ 100 mmHg (see text).
All regression coefficients were significant except that for age in women 5-year survivors at the 5-year examination.

at entry to the study. Significant differences in the mean chest diameter were found in all groups except men of 70 years and over. Differences in the mean cardiothoracic ratio occurred in both groups of men ($P < 0·05$) and of women ($P < 0·001$). When the signs of the differences are taken into account, the findings of the analysis are increases with age in mean heart size estimated by the cardiothoracic ratio in all groups, but increases in mean cardiac diameter only in older men and younger women. The difference in behaviour of these two variables is the result of the different levels of decrease in transverse chest diameter (Table 1). The large number of missing values of transverse chest diameter is the result of failure to include the whole width of male thoraces on some of the films taken at the original examination.

Data collected at the original examination from all persons taking part then, except those with diastolic blood pressure of 100 mmHg or more, were used to derive an equation to predict transverse cardiac diameter from age and body weight (Milne and Lauder, 1974). The regression coefficients are shown in Table 2, rows 1 and 5.

A similar equation was derived, for 5-year survivors, with age and body weight as the independent variables, using the data which had been collected at the original examination (Table 2, rows 2 and 6). In men the regression coefficients were similar to those in the first equation based on the whole sample, while in women, though the coefficient of regression on body weight was similar, the coefficient of regression on age was about half the value of that in the equation based on the whole sample.

An equation was similarly derived, using data obtained at the original examination from persons who died during the 5 years of the study (Table 2, rows 3 and 7); again regression coefficients in men resembled those in the first equation in Table 2, but in women the coefficient of regression on age was larger than that in the first equation. These differences in the coefficients of regression on age in women, though not statistically significant, suggest larger cardiac diameters in older women who died.

Finally, the regression of transverse cardiac diameter on age and body weight was calculated in surviving men and women using data gathered at the 5-year examination (Table 2, rows 4 and 8). Once again in men the regression coefficients were similar to those in the first equation in Table 2 but in women age ceased to make a significant contribution to the regression. This again suggested a loss from the sample of older women with larger hearts.

To test this hypothesis the regressions of transverse cardiac diameter on age and body weight based on the original data (Table 2, rows 1 and 4) were used to calculate the expected cardiac diameter in survivors examined 5 years after the original examination. The age used in the equation was age at entry plus 5 years. This predicted value was subtracted in each subject from the transverse cardiac diameter recorded at the 5-year examination (Table 3). This Table shows reasonable agreement between predicted and actual values except in women aged 70 years and over at original examination, in whom the mean predicted value was significantly larger than the mean recorded value.

The mean cardiac diameter was next examined using the original data, in the dead and in the survivors of men and women in both age groups on entry to the study. These survivors were not only those re-examined after 5 years but also included those who survived and after the first examination

TABLE 3 *Transverse cardiac diameter in older men and women recorded after 5 years minus diameter predicted from the regression on age† and weight based on original data*

| *Sex and age (at entry)* | *Mean difference (mm)* | *SD* | *No. of cases* |
|---|---|---|---|
| *Men* | | | |
| 62 to 69 y | −0·977 | 12·315 | 69 |
| ≥70 y | 1·608 | 12·191 | 39 |
| *Women* | | | |
| 62 to 69 y | 0·323 | 9·984 | 76 |
| ≥70 y | −3·631* | 9·957 | 44 |

*P<0·05.

†Age used in regression equals age at entry + 5 years.

TABLE 4 *Transverse cardiac diameter at original examination in two age groups of men and women separated into those who died and those who were alive 5 years later*

| *Sex and age (at entry)* | *Alive Mean (mm)* | *SE* | *No. of cases* | *Dead Mean (mm)* | *SE* | *No. of cases* |
|---|---|---|---|---|---|---|
| *Men* | | | | | | |
| 62 to 69 y | 136·2 | 1·50 | 88 | 139·0 | 2·91 | 33 |
| ≥70 y | 142·6 | 1·96 | 49 | 136·7 | 2·21 | 41 |
| *Women* | | | | | | |
| 62 to 69 y | 128·2 | 1·18 | 118 | 129·5 | 5·66 | 16 |
| ≥70 y | 128·8 | 1·36 | 86 | 139·7** | 2·30 | 37 |

**P<0·01.

were lost to the study for reasons other than death. Table 4 gives mean values with standard errors for these groups. The mean values in the dead and the survivors did not differ significantly except in women of 70 years and over (P < 0·01, two-tail test). In this group the mean cardiac diameter of the dead women appeared to be larger than that of the survivors. This confirmed the impression, described above, gained from studying coefficients of regression of cardiac diameter on age, using the data from the original examination, in women who survived for 5 years and in those who died.

TABLE 5 *Transverse cardiac diameter related to cause of death in two age groups of older men and women*

| *Sex and age (at entry)* | *Cause of death* | *Cardiac diameter Mean (mm)* | *SD* | *No. of cases* |
|---|---|---|---|---|
| *Men* | | | | |
| 62 to 69 y | Heart disease | 142·4 | 20·01 | 11 |
| | No heart disease | 140·1 | 15·51 | 20 |
| ≥70 y | Heart disease | 140·8 | 12·35 | 12 |
| | No heart disease | 134·9 | 14·63 | 29 |
| *Women* | | | | |
| 62 to 69 y | Heart disease | (152·0) | — | (2) |
| | No heart disease | 126·3 | 16·70 | 14 |
| ≥70 y | Heart disease | 148·1 | 14·87 | 14 |
| | No heart disease | 134·5 | 11·02 | 22 |

Mean cardiac diameters were compared in men and in women, aged 62 to 69 and 70 years and over on entry to the study, who were recorded as dying of heart disease and of diseases other than heart disease during the subsequent 5 years (Table 5). A significant difference (P < 0·05) in the transverse cardiac diameter was found only comparing women of 70 years and over who died of heart disease with those who died of another cause. In these women the mean transverse cardiac diameter was larger in the group who died of heart disease; no significant difference was found in the other three groups.

## Discussion

This study has confirmed from a 5-year follow-up what was suspected from cross-sectional data (Milne and Lauder, 1974), namely that the cardiothoracic ratio overestimates changes in heart size in the elderly. The data given above suggest that this is because of decrease in transverse thoracic diameter in many people as age increases. Other workers have also thought, on the basis of cross-sectional studies, that transverse thoracic diameter decreases with increasing age (Cowan, 1959; Mayer, Blazsik, and Rappaport, 1958; Edge *et al.*, 1964) but longitudinal studies such as the present one are a more certain method of confirming the hypothesis.

The various methods of data analysis used above suggested that the greatest difference between changes in cardiac diameter predicted from age differences in a cross-sectional study of the elderly and the actual changes recorded after 5 years, was found in women 70 years and over on entry to the study. This resulted from the death of women in this age group who had larger cardiac diameters. In the same age group of women the mean cardiac diameter was larger in those whose deaths were the result of heart disease than in those whose deaths were from other causes.

The regression of transverse cardiac diameter on age and weight based on cross-sectional data from men in the present study has been a reasonable predictor of changes in cardiac diameter over 5 years. In women a similar equation predicted 5-year changes greater than those that actually occurred. The loss by death of older women with larger cardiac diameters eliminated age from the regression in the survivors. Though the present study offers no confirmatory data, one might speculate that the difference described between men and women was a reflection of different time relations in the sexes between heart disease and mortality.

The increase in transverse cardiac diameter over 5 years in women aged 62 to 69 years at entry to the study does not preclude the possibility that the relation observed in this sample between transverse cardiac diameter and mortality in women aged 70 years and over at entry to the study may be a general phenomenon in the female population.

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# Hypertrophic cardiomyopathy in Friedreich's ataxia

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*The cardiac findings in two sibs with Friedreich's ataxia are described. The clinical signs were suggestive of hypertrophic obstructive cardiomyopathy. During left heart catheterization a systolic pressure gradient across the left ventricular outflow tract could be provoked by an infusion of isoprenaline. Left ventricular angiocardiograms and echocardiograms showed gross thickening of the interventricular septum. In one patient a systolic anterior movement of the anterior leaflet of the mitral valve was seen. The importance of serial echocardiographic examination for patients with Friedreich's ataxia is emphasized.*

The association of myocardial disease with the neurological signs of progressive ataxia has been known for many years. In his original publication Friedreich (1863) mentioned 'severe fatty degeneration of the musculature of the left ventricle' in his necropsy report on 3 patients. That this association is almost invariable is shown by the pathological findings in 16 cases reported by Hewer (1969). All hearts examined were abnormal and showed muscle fibre hypertrophy and interstitial fibrosis. The high incidence of cardiac involvement in postmortem series may be explained by the fact that the vast majority of patients with Friedreich's ataxia die from cardiac complications, mainly intractable cardiac failure or rhythm disturbances, rather than from their neurological disorder. In clinical series electrocardiographic changes are usually described as the first sign of cardiac involvement, often several years before the development of cardiomegaly and heart failure.

Little attention has been paid to the haemodynamic findings in this rare and ill-understood neurocardiac syndrome. Right heart catheterization usually does not show any significant abnormality. Recent reports (Soulié *et al.*, 1965; Boehm, Dickerson, and Glasser, 1970; Gach, Andriange, and Franck, 1971) on left heart catheterization and angiocardiography have indicated that there is a striking similarity between the findings in the cardiomyopathy of Friedreich's ataxia and in hypertrophic obstructive cardiomyopathy (idiopathic hypertrophic subaortic stenosis). In this report, we describe two sibs with Friedreich's ataxia in whom the clinical, haemodynamic, and echocardiographic findings of hypertrophic cardiomyopathy were present.

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## Observations

### Case 1

This boy, born 14 December 1955, was first evaluated at the age of 14 years because of a heart murmur, discovered at routine examination. When he was 7 years old the parents had first noticed that he had an unsteady gait and slurring of his speech. A few months before the examination he had to give up his training in a technical school because of progressive staggering and clumsiness. He tired easily on exertion. He has three brothers, one of whom (Case 2) presented with similar neurological symptoms. One of his two sisters suffers from epileptic attacks but is otherwise normal. One of his mother's first cousins died at the age of 30 years, allegedly from 'muscle weakness'.

On physical examination he was a thin boy with moderate kyphoscoliosis and generalized muscular dystrophy. Neurological examination showed the following abnormalities: slurring of speech, normal cranial nerves, ataxic gait, positive Romberg's sign, diminished muscle strength of the flexors of the legs and plantar flexors of the feet, weak tendon reflexes, particularly in the arms, normal superficial sensation, impaired vibration sense in the knees and iliac crests, and poor performance of finger pursuit

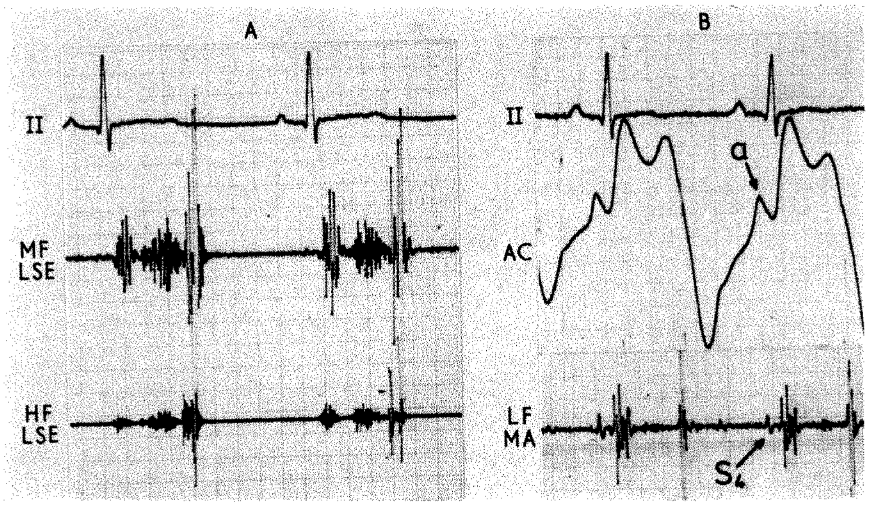

FIG. 1 *Phonocardiogram from Case 1. (A) Lead II of electrocardiogram, medium-frequency (MF) and high-frequency (HF) recording from left sternal edge (LSE). Note that the ejection murmur reaches its maximum intensity relatively late, well beyond the middle of systole (defined as the interval from the first sound to the aortic component of the second sound). (B) Lead II of electrocardiogram, apex cardiogram (AC), and low-frequency phonocardiogram (LF) from mitral area (MA). An intense fourth sound (S4) coincides with a prominent* a *wave on the apexcardiogram. Both phenomena suggest decreased left ventricular compliance.*

and heel-to-knee tests. There was no pes excavatus deformity. The arterial pulse was forceful and regular. Blood pressure was 120/70 mmHg. A heaving left ventricular impulse was felt 1 cm outside the midclavicular line. Jugular venous pressure was normal. A grade 3/6 midsystolic murmur was heard at the lower left sternal border and the apex. Splitting of the second sound was normal.

The phonocardiographic pattern of the murmur (Fig. 1) was diamond-shaped with its maximum intensity just before the middle of systole (defined as the interval from the first sound to the aortic component of the second sound). A loud atrial sound at the apex coincided with a prominent *a* wave on the apex cardiogram. A third sound was also recorded. The shape of the external carotid tracing was normal and did not show a pseudo-incisura. After the inhalation of amyl nitrite the intensity of the systolic murmur increased conspicuously. The downstroke on the carotid tracing became abrupt and the incisura less distinct.

The electrocardiogram (Fig. 2) showed regular sinus rhythm, a mean QRS axis of +70°, a prominent P wave (3 mm) in II, and tall R waves in V5 (30 mm) and V6 (24 mm). Sharply inverted T waves were seen in II, III, aVF, V4, V5, and V6. The chest *x*-ray film was within normal limits.

Cardiac catheterization (Table) under local anaesthesia showed normal systolic pressures and no gradient across the right ventricular outflow tract. The end-diastolic pressure in the right ventricle was slightly raised (8 mmHg). Arterial catheterization from the right brachial artery showed no pressure gradient between the left ventricle and the aorta. After an intravenous infusion of a small dose of isoprenaline (2μg/min for 3 minutes) the pressure in the left ventricle rose to 180/25 mmHg with a gradient of 70 mmHg on withdrawal to the ascending aorta.

Left ventricular biplane angiocardiograms (Fig. 3) showed several features characteristic of hypertrophic obstructive cardiomyopathy. The frontal view showed a small slit-like ventricular cavity in the end-systolic phase, a grossly thickened ventricular wall, and some indentation of its left upper portion in diastole. In the lateral systolic view a sharp angulation between the apex and the outflow tract was seen. The latter was narrowed by bulging of the hypertrophied interventricular septum opposite the anterior leaflet of the mitral valve. In diastole the narrowed subvalvar zone appeared as an inverted cone. There was no mitral regurgitation. The coronary arteries were large and dilated.

The echocardiogram[1] (Fig. 4) showed gross

[1] Echocardiovisor with multiscan and M-mode scan facilities and Honeywell no. 1856 strip chart recorder.

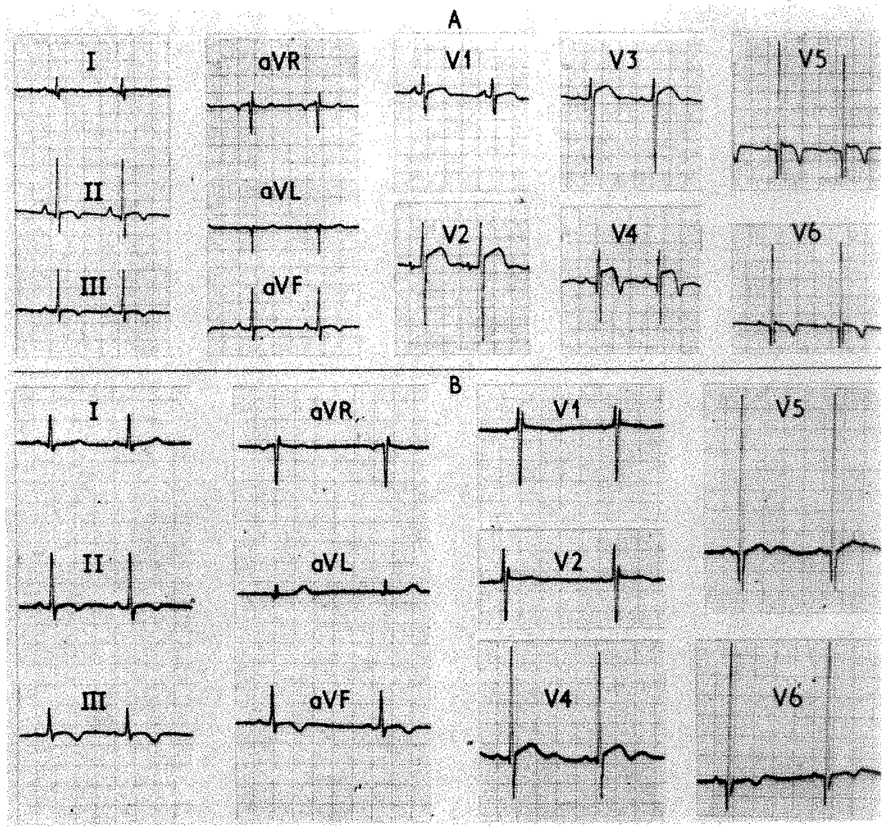

FIG. 2 *Electrocardiogram from two sibs with Friedreich's ataxia. (A) Case 1, (B) Case 2. The records both show left ventricular hypertrophy and pronounced ST segment changes, and are very similar.*

thickening of the interventricular septum (32 mm in end-diastole, 36 mm in systole) and the posterior left ventricular wall (22 mm). The septal posterior left ventricular wall ratio was 1·4:1. The transverse dimension of the left ventricular cavity, measured in the plane of maximal excursion of the mitral valve, was reduced (26 mm in end-diastole). Prominent systolic anterior movement (SAM) of the anterior leaflet of the mitral valve was recorded. Amyl nitrite inhalation enhanced the abnormal valve motion and produced almost complete occlusion of the outflow tract (Fig. 5).

## Case 2

This boy, brother of the previous patient, was born 11 October 1960. Symptoms of mild ataxia first appeared at the age of 12. Fatigue on exertion was his only complaint. When he was first examined at 13 years of age his appearance, asthenic body build, kyphoscoliosis, and unsteady gait gave him a striking resemblance to his older brother. Neurological examination showed the following: intermittent nystagmus, positive Romberg's sign, coordination only slightly impaired, hypotonia in upper and lower limbs, tendon reflexes much diminished in the arms but present in the legs, abdominal and cremasteric reflexes hyperactive, and normal superficial sensation and vibration sense. There was no pes cavus. On the whole the neurological disturbances were similar to those observed in his brother but seemed less severe. A grade 3/6 midsystolic murmur, preceded by an ejection sound, was best heard at the lower left sternal edge and the apex. It became much louder after the inhalation of amyl nitrite. The blood pressure was 120/65 mmHg.

The electrocardiogram (Fig. 2) showed considerable left ventricular hypertrophy in the

TABLE *Cardiac catheterization* data from two sibs with Friedreich's ataxia*

| | *RA* | *RV* | *PA* | *PA wedge* | *LV* | *Ao* |
|---|---|---|---|---|---|---|
| Case 1 | | | | | | |
| At rest | *a* 7<br>mean 4 | 24/8 | 24/12 | mean 10 | 105/16 | 105/70 |
| After isoprenaline | — | — | — | — | 180/20 | 110/65 |
| Case 2 | | | | | | |
| At rest | *a* 6<br>mean 4 | 18/4 | 14/7 | mean 11 | 110/10 | 100/65 |
| After isoprenaline | — | — | — | — | 135/10 | 100/52 |

*Pressures in mmHg.
*Abbreviations:* RA, right atrium; RV, right ventricle; PA, pulmonary artery; LV, left ventricle; Ao, ascending aorta.

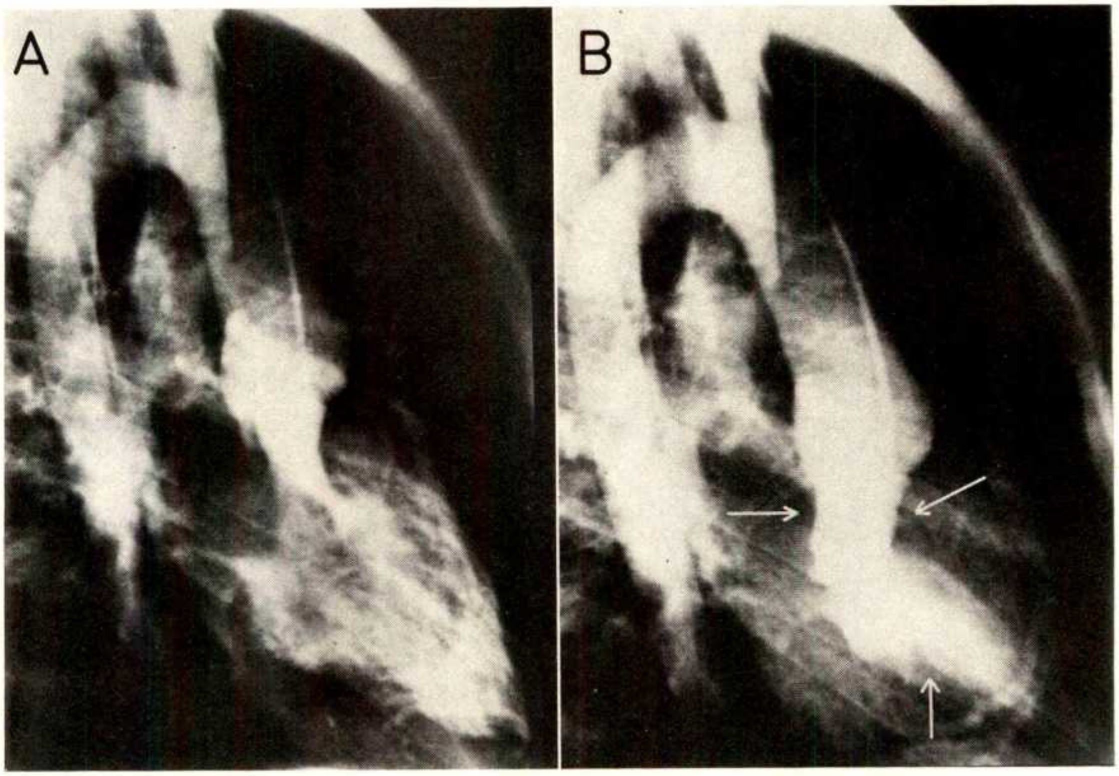

FIG. 3 *Lateral view of left ventricular angiocardiogram in Case 1. In diastole (A) the left ventricular outflow tract fails to open completely and has the appearance of an inverted cone beneath the aortic valve. Irregular translucent areas are produced by masses of hypertrophied myocardium. In systole (B) an angulation is seen between the body and the outflow tract. The latter is narrowed by bulging of the hypertrophied interventricular septum (oblique arrow) opposite the anterior leaflet of the mitral valve (horizontal arrow). Note the indentation produced by the hypertrophied posterior papillary muscle (vertical arrow). There is no mitral regurgitation.*

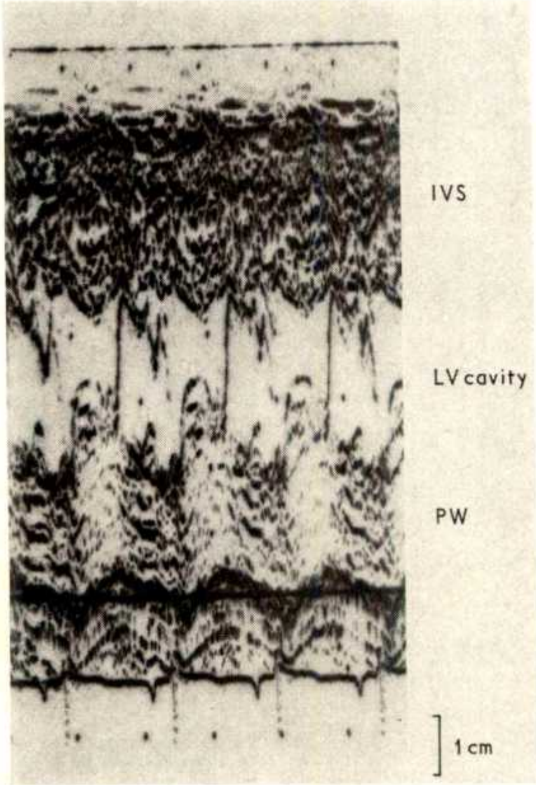

FIG. 4 *Echocardiogram obtained in Case 1. Gross thickening of the interventricular septum (IVS) is seen. The dimension of the left ventricular (LV) cavity is reduced. The irregular echo of the endocardial surface of the left ventricular posterior wall (PW) is probably partly produced by abnormally positioned papillary muscles. Note the systolic anterior movement of the mitral valve which further reduces the ventricular cavity.*

←

praecordial leads (32 mm R in V6). The T wave was slightly inverted in II, III, aVF, and the left praecordial leads. The chest *x*-ray was unremarkable.

At right heart catheterization (Table) normal pressures and oxygen saturations were found. Left heart catheterization from the right brachial artery showed no systolic gradient across the left ventricular outflow tract. During an infusion of isoprenaline (2μg/min) the left ventricular systolic pressure quickly rose from 110 to 135 mmHg while the aortic systolic pressure was unchanged (100 mmHg). Left ventricular cineangiocardiograms showed the same characteristics as in Case 1: very small end-systolic volume, thick ventricular wall, sharp angulation between the body of the left ventricle and its outflow tract, subvalvar narrowing

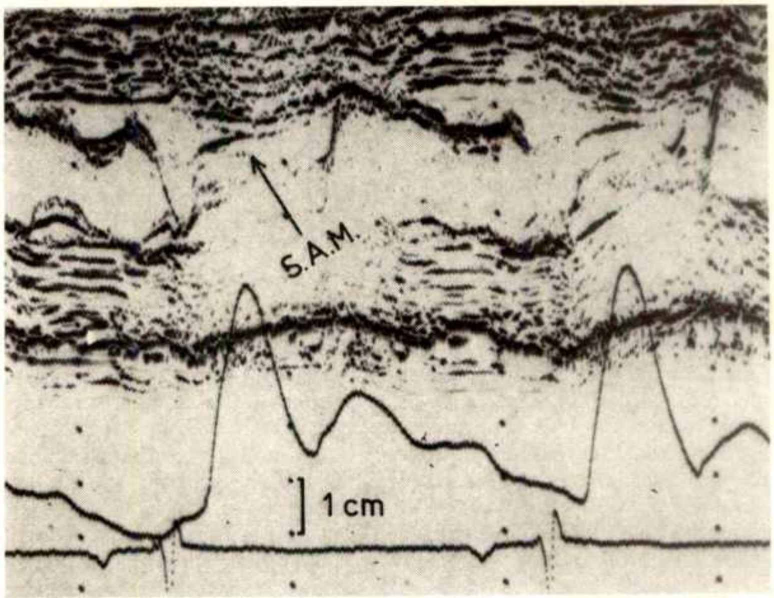

FIG. 5 *Detail of left ventricular echocardiogram in Case 1, after inhalation of amyl nitrite. The systolic anterior movement of the mitral valve (SAM) is greatly enhanced so that the anterior leaflet and the septum are in close apposition. Sweep speed is 50 mm/s.*

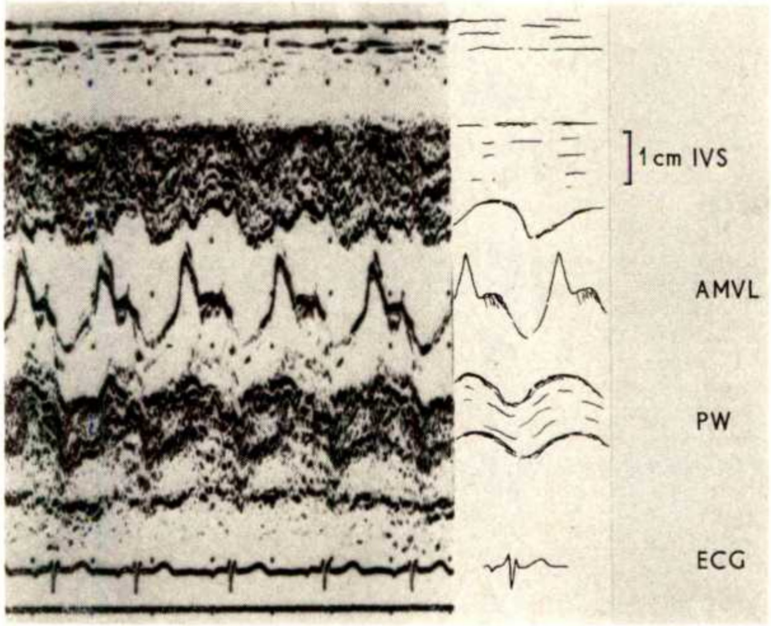

FIG. 6 *Echocardiogram from Case 2 showing thickening of the interventricular septum (IVS) in the presence of a normal posterior left ventricular wall (PW). The movement of the anterior leaflet of the mitral valve (AMVL) is normal.*

produced by septal hypertrophy, and the displaced anterior leaflet of the mitral valve.

The echocardiogram (Fig. 6) showed a thickened interventricular septum (17 mm in end-diastole and 23 mm in systole) with a normal posterior left ventricular wall (10 mm). The septal/posterior left ventricular wall ratio was thus 1·7:1. The transverse dimension of the left ventricular cavity (36 mm) was at the lower limit of normal. In contrast with the previous patient no systolic anterior movement of the mitral valve was observed, nor could it be provoked by inhalation of amyl nitrite.

## Discussion

In 2 sibs with Friedreich's ataxia signs characteristic of hypertrophic cardiomyopathy were found. A moderately loud midsystolic murmur was heard at the lower left sternal border and the apex. Its intensity increased after inhalation of amyl nitrite. An atrial sound and a prominent *a* wave on the apex cardiogram suggested decreased left ventricular compliance. In the older brother raised right and left ventricular end-diastolic pressures were recorded. At rest there were no gradients across the ventricular outflow tracts. During isoprenaline infusion, however, one patient developed a 70 mmHg pressure gradient, and the other a 35 mmHg gradient between the left ventricle and the aorta. Left ventricular angiocardiograms showed the radiological changes usually seen in hypertrophic obstructive cardiomyopathy (Cohen *et al.,* 1964: Simon, Ross, and Gault, 1967).

As far as we know, echocardiographic studies in this condition have not been published. In both patients the most striking feature was the gross thickening of the interventricular septum with an abnormal septal/posterior left ventricular free wall ratio of 1·4:1 in the older and 1·7:1 in the younger brother. In normal subjects, in fixed left ventricular outflow obstruction, and in miscellaneous heart diseases, Henry, Clark, and Epstein (1973a) found that this ratio was approximately 1:1. In all 15 patients with 'idiopathic hypertrophic subaortic stenosis', including 7 patients without a gradient under basal conditions, examined by these authors, the ratio exceeded 1·3:1. In both our patients the end-diastolic transverse dimension of the left ventricle was reduced (26 mm in one and 36 mm in the other patient) as compared with the measurements in normal subjects (Henry *et al.,* 1975). Finally, in the older patient, who was more severely affected, a characteristic systolic anterior movement of the anterior mitral valve leaflet, as described in hypertrophic obstructive cardiomyopathy (Shah, Gramiak, and Kramer, 1969; Pridie and Oakley, 1969) and in asymmetrical septal hypertrophy (Henry *et al.*, 1973a, 1975) was seen. The amplitude and duration of this abnormal valve movement could be greatly enhanced by the inhalation of amyl nitrite (Fig. 5). In the other patient no such valve movement could be recorded under basal conditions, nor could it be provoked.

Obviously the obstructive character of the cardiomyopathy in Friedreich's ataxia may easily be missed if not specifically looked for. Thorén (1964), who reported the results of right heart catheterization in 17 patients, mentioned raised end-diastolic pressures and a prominent *a* wave in the most advanced cases. Though he found no significant gradients across the infundibulum (left heart catheterization and pharmacological tests were not performed), he commented on the gross right ventricular hypertrophy and systolic narrowing of the infundibulum. This made him speculate that 'there is reason to compare this myocardial disease with the co-called stenosing and isolated myocardial hypertrophy'. Soulié *et al.* (1965) were probably the first to observe outflow tract obstruction in patients with Friedreich's ataxia. In 1 of the 4 patients who underwent cardiac catheterization, a gradient in both the right and left ventricular outflow tracts was found. In one patient Moore and Lambert (1968) found normal pressures under basal conditions but were able to provoke gradients in both outflow tracts by an infusion of isoprenaline. A similar observation was reported by Boehm *et al.* (1970) and by Gach *et al.* (1971). In the latter study the diagnosis of obstructive hypertrophic cardiomyopathy was confirmed by right and left ventricular angiocardiograms. They showed dynamic infundibular narrowing in the right ventricle and a funnel-shaped subvalvar stenosis in the left ventricle, produced by encroachment of a thick interventricular septum and an anteriorly displaced anterior leaflet of the mitral valve. A slight degree of mitral regurgitation was noted.

That outflow tract obstruction is not invariably associated with Friedreich's cardiomyopathy is borne out by the report of Ruschhaupt, Thilenius, and Cassels (1972). Having observed one child with severe hypertrophic subaortic stenosis, they undertook a haemodynamic study in 5 other children with Friedreich's ataxia. Right and left heart pressures were normal in all patients. Only in one patient could a 40 mmHg pressure gradient across the left ventricular outflow tract be induced by an infusion of isoprenaline.

It is very unlikely that the occasional occurrence of outflow tract obstruction in Friedreich's ataxia is related to any specific metabolic or neurogenic disturbance in this condition. Obstructive cardiomyopathy has indeed been described in the course of various disorders which, as far as we know, have no common aetiological basis. Sporadic examples have been reported in association with glycogen storage disease (Ehlers *et al.*, 1962), lentiginosis (Somerville and Bonham-Carter, 1972), Noonan's syndrome (Ehlers *et al.*, 1972), and Refsum's disease (Pernot, Tridon, and Henry, 1973). From these cases and from a number of reports on cardiomyopathy in Friedreich's ataxia, including our own observations, it appears that the haemodynamic and angiocardiographic features are indistinguishable from those seen in isolated hypertrophic obstructive cardiomyopathy, whether familial or sporadic. One is entitled, therefore, to consider the obstructive 'reaction' as non-specific. It probably reflects the severity of the myocardial hypertrophy, whatever the cause, and particularly its distribution within the myocardium. It is generally agreed that major involvement of the interventricular septum produces asymmetrical hypertrophy and therefore tends to cause left ventricular outflow obstruction (Goodwin and Oakley, 1972; Henry, Clark, and Epstein, 1973b) whereas thickening of the free wall of the left ventricle would lead to non-obstructive hypertrophic cardiomyopathy. In the present study and on previously published left ventricular angiocardiograms (Gach *et al.*, 1971), hypertrophy of the interventricular septum seemed to be a striking feature. Furthermore, the echocardiograms in our patients showed the characteristic abnormalities of asymmetrical septal hypertrophy (Henry *et al.*, 1973a). In the older patient, in whom the disease was more advanced, echocardiographic evidence of left ventricular outflow obstruction at rest was found.

One may speculate that our patients represent two stages of a slowly progressive form of hypertrophic cardiomyopathy characterized by asymmetrical septal hypertrophy and a variable degree of left ventricular outflow obstruction. More follow-up studies in a larger number of patients with Friedreich's ataxia are needed to corroborate this view. Because it is noninvasive, echocardiography seems to be the method of choice for these future studies.

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# Effect of oestrogens on postexercise electrocardiogram

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*The effect of three oestrogens (including an oestrogen-progestogen combination) on the postexercise electrocardiogram was studied in 33 men and 18 women who earlier had shown ST segment abnormalities after exercise. When pretreatment exercise tests were compared with tests after two weeks of treatment, the postexercise ST segments which were abnormal before treatment became even more abnormal in 18 (90%) of 20 subjects treated with conjugated oestrogens 10 mg daily, in 16 (89%) of 18 subjects treated with stilboestrol 5 mg daily, and in 12 (92%) of 13 subjects treated with norethynodrel (9·85 mg) and mestranol (0·15 mg)[1] daily. The ST segment abnormalities reverted to pretreatment appearance within 6 weeks of stopping oestrogens. When 10 subjects with normal near-maximal exercise tests were treated for 2 weeks with conjugated oestrogens 10 mg daily, the tests remained unchanged in 9.*

*The hypothesis favoured to explain these findings is that of an oestrogen-induced increase in coronary artery smooth muscle tone. An increase in arterial tone would also account for the increased incidence of myocardial (and cerebral) infarction that has been reported among individuals treated with oestrogen, either alone or in combination with progestogen.*

The reason premenopausal women have a lower incidence of death from myocardial infarction than men of similar age is not understood (Stamler, 1967). That oestrogen alone affords this protection against myocardial infarction seems unlikely in view of the fact that oestrogen administration has been shown to be associated with an increased incidence of myocardial infarction (Robinson, Higano, and Cohen, 1963; McDowell, Louis, and McDevitt, 1967; Blackard *et al.*, 1970; Coronary Drug Project Research Group, 1970) and also of stroke (Robinson *et al.*, 1963; McDowell *et al.*, 1967; Blackard *et al.*, 1970). Administration of oestrogens with progestogens in the form of oral contraceptive agents has also been associated with myocardial infarction (Waxler *et al.*, 1971; Dear and Jones, 1971; Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975) and stroke (Masi and Dugdale, 1970; Dalessio, 1972; Collaborative Group for the Study of Stroke in Young Women, 1973; Horenstein, 1975). There has been no generally acceptable explanation for these findings.

If oestrogens induce changes in the circulation even before infarction, recognition of these changes might offer new insights into the little understood relation between sex hormones and coronary heart disease. It was reasoned that the postexercise electrocardiogram reflects the capability of the coronary arteries (including collaterals) to deliver blood to meet myocardial oxygen needs for any given exercise load. An effect of oestrogen on the coronary circulation might, therefore, be shown by changes in the postexercise electrocardiogram. In this study, the effect of three oestrogens (including an oestrogen-progestogen combination) was assessed by this technique.

## Patients and methods

The effect of oestrogens on the postexercise electrocardiogram was studied in 33 men and 18 women who had previously been shown to have an abnormal electrocardiographic response to exercise. Their ages ranged from 40 to 70 years (mean 57). Eighteen subjects had had a previous myocardial infarction confirmed by an abnormal Q wave on the electrocardiogram or by a clinical course (including cardiac enzyme changes) suggesting infarction; 38 had stable, characteristic, but not in-

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[1] Enovid (Searle).

capacitating angina pectoris; 30 were receiving treatment for hypertension (diastolic pressure ⩾90 mmHg) and 19 for diabetes mellitus. Subjects with incapacitating angina pectoris, the 'intermediate coronary syndrome', or cerebrovascular insufficiency were excluded because of the concern that myocardial infarction or stroke might be precipitated by oestrogen administration. Subjects with an organic heart murmur, overt congestive heart failure, or electrocardiographic evidence of left ventricular hypertrophy, intraventricular conduction defect (QRS duration ⩾0·12 s), or atrial fibrillation, and those receiving digitalis, quinidine, procainamide, or propranolol were also excluded.

A two-step exercise test was used employing a rate and duration (usually between 3 and 6 minutes) of exercise for each subject, which would result in an abnormal postexercise ST segment response. The two-step test rather than a graded exercise test was used for this study because of our previous experience in evaluating other therapeutic interventions using this test. Horizontal or downsloping ST segment depression of 0·1 mV (1 mm) or more not present on the pre-exercise tracing was the single criterion by which the electrocardiographic response to exercise was termed abnormal: this occurred in 48 subjects. Horizontal or downsloping ST segment depression of at least 0·5 mm but less than 1 mm was termed possibly abnormal: this occurred in 3 subjects.

At least three exercise tests were obtained before starting treatment. The tests were carried out with the object of selecting subjects, establishing individual test workloads, and eliminating the possibility of improvement in exercise test performance resulting from a training effect. The last postexercise electrocardiogram before treatment (baseline) was compared with that recorded at the completion of two weeks of oestrogen treatment, when exercise was performed at the same rate and for the same time as during the baseline test. In addition, in 24 of the 51 subjects similar testing was performed 4 to 6 weeks after treatment was completed, and this postexercise electrocardiogram was compared with the baseline recording and that obtained after two weeks of oestrogen treatment.

A standard 12-lead resting electrocardiogram was recorded before each exercise test. Leads II, V4, V5, and V6 were recorded immediately, 2, 4, and 6 minutes after exercise and at additional intervals if needed until the electrocardiogram returned to the pre-exercise appearance. Brachial cuff blood pressures were obtained with the subject in the supine position before exercise and immediately after exercise. Each test in a series was performed at about the same time of day as the others, and at least four hours after a meal. Exercise and work routines, food intake, and drug treatment were maintained at a constant level between tests. No short or long acting 'coronary vasodilators' were taken by the subjects during the 12 hours before exercise testing.

Before starting treatment and after the nature of the study and possible effects of the drugs had been thoroughly discussed, written informed consent was obtained from each subject.

At the time the postexercise ST segment of the baseline and post-treatment recordings were compared and the differences between them recorded, the recordings were identified only by a code which was unknown to the observer. The code was then broken in order to determine which recordings were baseline and which were post-treatment. Grading was as follows:

*Grade 0:* No change in ST segment slope or depression as compared with the corresponding baseline recording after exercise.

*Grade 1:* Decrease of the ST segment slope. To be so classified, an upsloping ST segment must have become horizontal or downsloping, or a horizontal ST segment must have become downsloping.

*Grade 2:* ST segment depression up to 1 mm greater than in the corresponding baseline tracing.

*Grade 3:* ST segment depression of 1 mm or more greater than in the corresponding baseline tracing.

Each of the 51 subjects was treated for two weeks with either conjugated oestrogens[1] 10 mg daily, stilboestrol 5 mg daily, or norethynodrel 9·85 mg with mestranol 0·15 mg (Enovid) daily.

Ten additional subjects (5 men; 5 women), selected from patients found to be free of evident disease on routine history and physical examination, who had a normal resting and postexercise electrocardiogram were treated with conjugated oestrogens 10 mg daily for 2 weeks and then retested.

## Results

The effect of conjugated oestrogens, 10 mg daily, on the electrocardiographic response to exercise was evaluated in 20 subjects of whom 17 had an abnormal and 3 a possibly abnormal exercise test before treatment. Eighteen (90%), including the 3 subjects with a possibly abnormal exercise test before treatment, showed an increase in postexercise ST segment changes after two weeks of treatment (Table).

Eighteen other subjects who had an abnormal exercise test before treatment were given stilboestrol, 5 mg daily (Table). Sixteen (89%)

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[1] USP

TABLE *Distribution of subjects according to degree of increase of postexercise ST segment abnormality after two weeks of hormone treatment*

| | *Increase of ST segment abnormality* | | | | |
|---|---|---|---|---|---|
| | *Grade* *0* | *1* | *2* | *3* | |
| | *No. of cases* (%) | *No.* (%) | *No.* (%) | *No.* (%) | *Total* |
| Conjugated oestrogens, 10 mg daily | 2 (10) | 11 (55) | 6 (30) | 1 (5) | 20 |
| Stilboestrol, 5 mg daily | 2 (11) | 6 (33) | 6 (33) | 4 (22) | 18 |
| Norethynodrel 9·85 mg + mestranol* 0·15 mg, 10 mg daily | 1 (8) | 3 (23) | 5 (38) | 4 (31) | 13 |
| All oestrogen-treated subjects | 5 (10) | 20 (39) | 17 (33) | 9 (18) | 51 |

*Enovid (Searle).

showed an increase in postexercise ST segment changes after 2 weeks of treatment.

Norethynodrel (9·85 mg) with mestranol (0·15 mg) (Enovid) was given daily to 13 additional subjects who had abnormal exercise tests before treatment (Table). Twelve (92%) showed increased postexercise ST segment changes after 2 weeks of treatment.

In 46 (90%) of the 51 subjects oestrogen treatment resulted in an increase in the postexercise ST segment abnormalities; in 5 (10%) of the 51 subjects there was no change; and in no instance did the ST segment abnormality lessen with treatment (Table). When 24 of the 51 subjects were tested again 4 to 6 weeks after oestrogens were stopped, it was found that the postexercise ST segment abnormalities had reverted to a pretreatment appearance in all.

The immediate postexercise heart rate of subjects in the three treatment groups before treatment was 131 ±5 (mean ±SEM) beats per minute and after treatment was essentially unchanged (132 ±4 beats per minute). The immediate postexercise systolic pressure before treatment was 162 ±6 mmHg and after treatment was 157 ±4 mmHg. This difference was not significant. The subjects averaged 0·5 kg weight gain with treatment. No myocardial infarction or stroke occurred with treatment.

Three subjects had previously had coronary arteriography. In two this showed the presence of obstructive coronary artery disease. The other, a 48-year-old man with angina pectoris and a possibly abnormal electrocardiographic response to exercise, had a normal coronary arteriogram. He was treated with conjugated oestrogens, 10 mg daily, which were discontinued after 5 days because of greatly increased frequency and severity of chest pain. An exercise test two days later showed an increase (grade 2) in ST segment abnormality after exercise.

Of the normal subjects who were treated for 2 weeks with conjugated oestrogens, 10 mg daily, 9 showed no change in the postexercise electrocardiogram after treatment and 1 developed a more horizontal ST segment (without ST segment depression) than before treatment.

## Discussion

Exercise-induced ST segment depression is usually considered evidence of myocardial ischaemia (Detry, 1973), though factors other than ischaemia may also produce these changes (Bruce, 1974; Lary and Goldschlager, 1974). Since most of the subjects in this study had clinically evident coronary heart disease as manifested by angina pectoris or a previous myocardial infarction, the postexercise ST segment changes in this group were probably the result of ischaemia in most instances.

That the increase in postexercise ST segment abnormality represents an incidental oestrogen-induced electrocardiographic abnormality is unlikely because none of the 10 subjects with normal stress tests developed postexercise ST segment depression when treated with oestrogen. Furthermore, the fact that oestrogen did not produce postexercise ST segment abnormalities in these normal subjects suggests that the reserve capacity of their coronary arteries was such that the adverse effect of oestrogens was insufficient to result in ischaemic electrocardiographic abnormalities after exercise. Oestrogen administration did, however, increase postexercise ST segment changes in subjects who earlier had an abnormal or a possibly abnormal electrocardiographic response to exercise. This is compatible with the view that oestrogen treatment further reduced an already diminished coronary blood flow.

This study shows that the postexercise ST segment abnormalities that are present before oestrogen treatment become even more pronounced immediately after treatment, and then revert to pretreatment appearance within the subsequent 6 weeks. Any hypothesis that is proposed to explain the mechanism of action of oestrogen on the circulation must be able to explain these findings and also explain the manner by which oestrogen predisposes to myocardial or cerebral infarction. The finding that the adverse effect of oestrogen on the circulation is reversible as long as infarction has not occurred tends to exclude a process that is essentially irreversible (e.g. accelerated atherogenesis or thrombus formation) as a mechanism of oestrogen action.

That oestrogen might act to increase myocardial oxygen requirements and thereby increase postexercise electrocardiographic abnormalities also seems unlikely because immediate postexercise systolic pressure and heart rate (which reflect oxygen need) were not higher after oestrogen treatment. The lack of significant weight gain after oestrogen treatment is evidence against a haemodilution effect or congestive heart failure as mechanisms underlying increased ST segment abnormalities.

Recently vascular spasm has been recognized as a possible mechanism leading to myocardial infarction (Cheng *et al.,* 1972; Carleton and Johnson, 1974; Sasse, Wagner, and Murray, 1975; Hellstrom, 1975; Ciraulo, 1975). Coronary arteriographic studies or necropsy of several women who experienced a myocardial infarction while receiving oral contraceptive agents did not show coronary atherosclerosis (Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975). Spasm (constriction caused by a large increase in vascular tone) has been suggested (Ciraulo, 1975) to be the mechanism underlying these infarctions and also underlying myocardial infarction during pregnancy in women with normal coronary arteriograms (Sasse *et al.,* 1975). If oestrogen acts to increase coronary arterial tone, spasm may result if this effect is sufficiently intense. In subjects with advanced coronary obstructive disease even a modest increase in tone might result in increased postexercise electrocardiographic abnormality and a further increase in tone might result in myocardial infarction.

Coronary artery spasm may produce angina pectoris (Demany, Tambe, and Zimmerman, 1968; Oliva, Potts, and Pluss, 1973; MacAlpin, 1973; Carleton and Johnson, 1974; Donsky *et al.,* 1975). Any increase in vascular tone narrows the arterial lumen and thereby decreases arterial blood flow capacity. In the present study oestrogen treatment increased the postexercise ST segment abnormalities in a subject with normal coronary arteries (shown by arteriography) as well as in subjects with obstructive coronary artery disease. If oestrogen results in an increase in coronary arterial (or arteriolar) tone, this mechanism would account for these findings as well as the finding that the oestrogen-induced abnormalities were lost within 6 weeks after oestrogen was stopped. An oestrogen-induced increase in coronary artery tone would also account for the occurrence of myocardial infarction in women on oral contraceptive agents (Waxler *et al.,* 1971; Dear and Jones, 1971; Maleki and Lange, 1973; Radford and Oliver, 1973; Ciraulo, 1975), and for the increased incidence of myocardial infarction in men receiving conjugated oestrogens, 5 mg daily (Coronary Drug Project Research Group, 1970), or stilboestrol, 5 mg daily (Blackard *et al.,* 1970).

When arterial smooth muscle contracts because of an increase in its tone, the degree of arterial constriction that results may be enhanced if the quantity of arterial smooth muscle is increased. Danforth, Manalo-Estrella, and Buckingham (1964) have shown that arterial smooth muscle mass increases in response to female hormones, for example during pregnancy or treatment with norethynodrel and mestranol. In this way, oestrogen treatment might further contribute to arterial constriction.

These considerations also apply to the cerebral circulation. Oestrogen treatment has been associated with an increased incidence of stroke (Robinson *et al.,* 1963; McDowell *et al.,* 1967; Blackard *et al.,* 1970). Oral contraceptive agents may exacerbate migraine headache which in some women has been followed by a stroke (Masi and Dugdale, 1970; Dalessio, 1972). Neurological symptoms in a migraine attack may be associated with spasm of the internal carotid artery or its branches and relieved by nitroglycerin (Adams and Griffith, 1970).

Oestrogen has been shown to increase contractility in the smooth muscle of the uterus (Pinto *et al.,* 1964) and to increase the responsiveness of smooth muscle in mesenteric arterioles to vasoactive hormones (Altura, 1973). However, an increase in smooth muscle tone of coronary or cerebral arteries in response to oestrogen treatment has not been studied directly. Nevertheless, an oestrogen-mediated increase in vascular smooth muscle tone accounts for the results of this study better than any other mechanism that has been considered.

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# Histopathology of conducting system in left anterior hemiblock

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*In 8 cases of left anterior hemiblock; combined with right bundle-branch block in 7, serial sections of the conducting system of the heart were examined histologically.*

*In all cases there were pathological changes in the left bundle-branch but the anterior part of it was predominantly affected in only 2 cases. Acute changes were found in 6 cases of early myocardial infarction, and fibrosis in 2 cases of chronic heart disease. Reversible lesions may have a pathogenetic role in acute hemiblocks. The right bundle-branch was disrupted by fibrosis in 6 of the 7 cases with right bundle-branch block, and minor changes in the AV node were observed in 1.*

*The widespread damage to the left bundle-branch in the majority of the present cases does not seem to be consistent with the limited clinicopathological correlation implied by the terms anterior fascicular block or hemiblock. Other cardiac lesions within the left bundle-branch and outside it may contribute to this electrocardiographic pattern.*

The use of the term 'left hemiblock' is based on the concept that there is anatomical and functional dichotomy of the left bundle-branch into an anterior and a posterior fascicle, and on the inferred trifascicular character of the conducting system (Rosenbaum, Elizari, and Lazzari, 1968; Rosenbaum *et al.*, 1970). This assumption that isolated block of one division of the left bundle-branch may occur alone or in combination with right bundle-branch block made it possible to give quick and easy answers to debated questions about intraventricular conduction defects and axis deviation (Pryor and Blount, 1966; Rosenbaum, 1970). This explains why the idea and the clear-cut terminology of hemiblock or fascicular block, implying disease of a discrete segment of the left bundle-branch system, have become popular among cardiologists.

This view was not shared by histopathologists, who criticized the original descriptions of hemiblocks on both anatomical and pathological grounds (Blondeau and Lenègre, 1970; Rossi, 1970, 1971; J. Lenègre, 1971, personal communication; Demoulin and Kulbertus, 1972). Sugiura *et al.* (1969) and Harris, Siew, and Lev (1969) appeared to accept the morphological basis of the concept of hemiblock, but later Lev has become critical of it (Hecht *et al.*, 1973).

Experimental studies have been reported in which the alleged twin ramifications of the left bundle-branch were separately cut (Medrano *et al.*, 1975), but in these studies the resulting lesions were not examined histologically, so that no light was shed on the actual morphological basis of the 'hemiblocks' which were produced (Rossi, 1975).

Anatomical, physiological, and pathological evidence casts doubt on the validity of the hemiblock concept. Anatomically, a definite subdivision of the left bundle-branch into two fascicles is uncommon in man. In most hearts the left bundle-branch is known to fan out into three distal strands, anterior, middle, and posterior (Rossi, 1971, 1974; Hecht *et al.*, 1973), freely anastomosing with one another, making it difficult to discern any anatomical and clear functional separation (Blondeau and Lenègre, 1970). Physiologically, left ventricular activation in the human heart starts simultaneously in three septo-paraseptal areas (Durrer *et al.*, 1970), suggesting three rather than two pathways of impulse distribution. Clinicophysiological studies by Kulbertus (1972) also suggested that it might be possible to distinguish conduction disturbances in the mid-septal group of left bundle-branch fibres. Finally, when the changes in the left bundle-branch

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were examined histologically in cases of hemiblock (Rossi, 1971; J. Lenègre, 1971, personal communication; Demoulin and Kulbertus, 1972; Rizzon *et al.,* 1975) there was no precise and constant correlation between the pathological and clinical observations.

Aware of these uncertainties, a committee of cardiologists appointed by the American College of Chest Physicians (Hecht *et al.,* 1973), convened to revise nomenclature and concepts of cardiac conduction, tried to discourage the use of the currently popular term 'hemiblock', both on morphological and functional grounds, so far with little success.

The aim of the present study is to re-examine the incidence, type, location, and possible clinicopathological significance of histological changes in the conducting system, particularly in the left bundle-branch, in cases of acute or chronic 'left anterior hemiblock'.

## Subjects and methods

The conducting system of the heart has been studied in 8 subjects with electrocardiographic signs of 'left anterior hemiblock' (the diagnostic criteria are those of Rosenbaum, 1970), alone in 1 case, combined with right bundle-branch block in 7, and with first or second degree AV block in 3. In 6 cases the conduction disturbances were observed during the course of recent myocardial infarction; in 2 cases they were associated with chronic heart disease. The main clinical and necropsy data are shown in the Table, and an illustrative electrocardiogram is reproduced in Fig. 1.

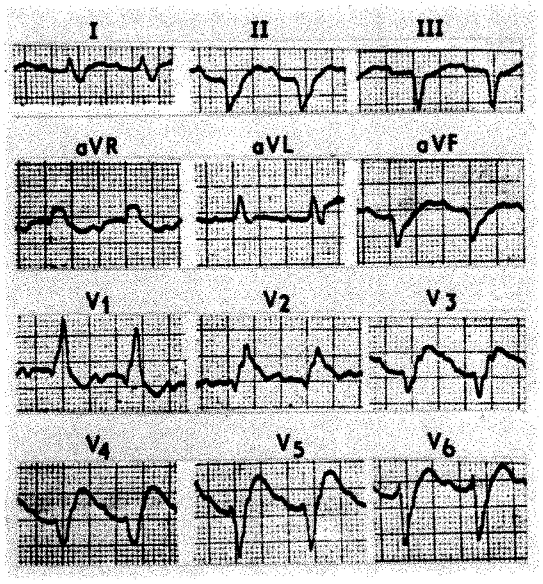

FIG. 1 *Case 2. Electrocardiogram showing acute anteroseptal myocardial infarction, with 'left anterior hemiblock', complete right bundle-branch block, and first degree AV block.*

From each heart, at necropsy, a single block of tissue was removed comprising the ventricular septum (or the upper 3/4 of it), the central fibrous body, and the lowermost part of the atrial septum. The block was fixed in formalin and embedded in paraffin; serial sections were cut at 150 $\mu$ intervals along the longitudinal plane of the septa, at right angles to their endocardial surfaces, and were stained with haematoxylin and eosin (H. and E.) or Azan stain to distinguish muscle from collagen. This technique was preferred to that of transverse sectioning of the septum, previously subdivided into several blocks (Demoulin and Kulbertus, 1972), in order to secure the best plane for the observation of the majority of the left bundle-branch fibres, sectioned along their main axis, and to examine the entire conducting system at the same time.

## Pathological findings

'Left anterior hemiblock', in the present cases, was constantly associated with pathological changes in the left bundle-branch. In 6 of the 7 cases with concomitant right bundle-branch block, the right bundle-branch was also severely damaged. No important lesions were observed elsewhere in the conducting system, except for slight fibrosis of the AV node in Case 6.

Impaired blood supply to the myocardium and conducting tissue, by severe atherosclerotic stenosis and/or thrombotic occlusion of major branches of the coronary tree, was found in all hearts except that of Case 7. The left coronary artery was predominantly affected; one case alone had an acute occlusion of the right (Case 4).

The histopathological changes in the left bundle-branch were not discrete and localized, but more widespread, affecting the left side of the ventricular septum and sometimes also the left ventricular walls, particularly when the left bundle-branch was involved in transmural or subendocardial septal infarction.

The lesions of the left bundle-branch were acute and/or subacute, whereas those of the right bundle-branch were always chronic (i.e. fibrotic). Disrupting atrophy and fibrosis of the left bundle-branch in Cases 6, 7, and 8 were not characteristic of Lenègre's or Lev's disease, whose importance in the pathology of hemiblocks has been emphasized

TABLE *Clinical and pathological summary of 8 cases of left anterior hemiblock*

| *Case No.* | *Age (y)* | *Sex* | *Conduction defects* | *Clinical and necropsy data* | *Conducting system histopathology* |
|---|---|---|---|---|---|
| 1 | 71 | F | LAH+RBBB | Diabetes, hypertension, acute anteroseptal infarction, and heart failure; death after 1 day (cardiac arrest); at necropsy, cardiac hypertrophy, coronary atherosclerosis, recent thrombotic occlusion of proximal left anterior descending coronary artery, with recent anteroseptal infarction | Diffuse oedema, leucocytic infiltration and vacuolar degeneration of lower half of LBB; patchy fibrosis of root and upper posterior radiations |
| 2 | 70 | M | LAH+RBBB and terminal 1st degree AV block | Early anteroseptal infarction with recurrent praecordial pain; death after 7 days (left ventricular failure); at necropsy, severe coronary atherosclerosis with severe stenosis of right coronary artery; acute and subacute changes of anteroseptal and posterior infarction | Severe degeneration and small necrotic patches, with leucocytic infiltration and early fibrosis of anterior part of LBB; oedema, vacuolar degeneration, leucocytic infiltration and haemorrhage of middle and posterior radiations; disruptive fibrosis of RBB |
| 3 | 58 | M | LAH+RBBB and terminal 2nd degree AV block | Recent posterior infarction; death after 7 days (ventricular fibrillation); at necropsy, cardiac hypertrophy, coronary atherosclerosis, posteroseptal infarction | Diffuse oedema, leucocytic infiltration and patchy haemorrhage of LBB, predominantly of anterior strands; subendocardial myocardial infarction; fibrosis of RBB |
| 4 | 86 | M | LAH+RBBB | Chronic heart disease and hypertension; recent extensive anterior infarction; death from cardiac arrest; at necropsy, anteroseptal and lateral infarction; recent thrombosis of proximal right coronary artery, and diffuse stenosis of left coronary artery | Slight fibrosis of posterior and middle strands with diffuse oedema and scattered leucocytic infiltration of LBB; subendocardial haemorrhage; fibrotic disruption of RBB |
| 5 | 72 | M | LAH+RBBB | Recent anteroseptal infarction with recurrent ventricular fibrillation; surgical infarctectomy 2 weeks after infarction, and death 16 hours later; at necropsy, cardiac hypertrophy, coronary atherosclerosis, subocclusive thrombosis of proximal left coronary artery; extensive anteroseptal infarction, with sutured surgical incision in anterior wall of left ventricle | Severe degeneration with patchy necrosis of LBB, predominantly of middle and posterior strands; extensive fibrotic disruption of RBB |
| 6 | 55 | M | LAH+RBBB and 1st degree AV block | Recent posterior infarction; death after three weeks (cardiac failure); at necropsy, subacute infarcts of left ventricle and extensive scarring of ventricular septum; severe coronary atherosclerosis | Extensive fibrotic involvement of distal part of LBB in post-infarction scarring, with oedema and vacuolization of surviving LBB fascicles; fibrotic interruption of proximal RBB; peripheral fibrosis of the AV node |
| 7 | 26 | M | LAH | Marfan syndrome; sudden death from ruptured dissecting aneurysm of aorta (confirmed at necropsy) | Atrophy and fibrosis of LBB fascicles, predominantly of middle and posterior radiations |
| 8 | 71 | M | LAH+RBBB | Chronic heart disease and hypertension; hemiplegia; death from chronic cardiac failure and pulmonary oedema; at necropsy, considerable cardiac hypertrophy and myocardial fibrosis, coronary atherosclerosis | Severe and diffuse fibrosis of LBB, slightly predominant in middle and posterior strands, fibrotic interruption of RBB |

*Abbreviations:* LAH: left anterior hemiblock; LBB, RBB: left and right bundle-branch; RBBB: right bundle-branch block.

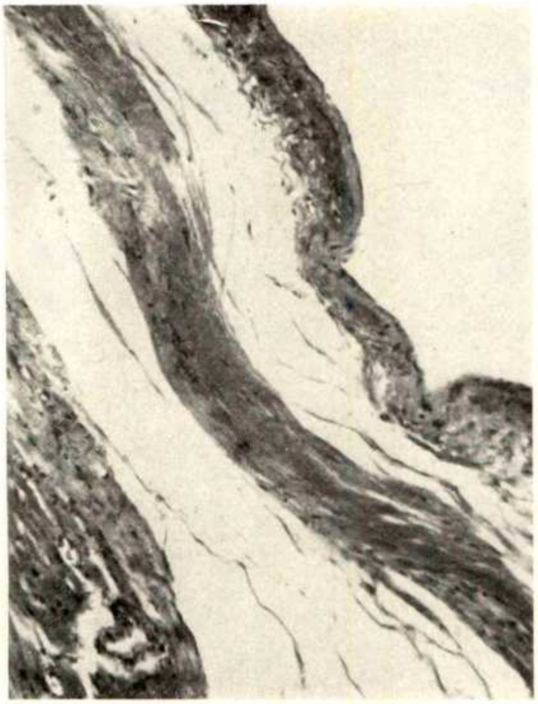

FIG. 2 *Case 5. Homogeneous acidophilia with loss of nuclei, from coagulative necrosis of the left bundle-branch in acute myocardial infarction. (H and E ×115.)*

by Rosenbaum *et al.* (1970). Acute, probably irreversible lesions, namely coagulative necrosis (Fig. 2) and advanced degeneration of myocardial cells, with extreme vacuolization, loss of the myofibrils and of the nucleus (Fig. 3 and 4), were predominant in Case 5, disrupting small fascicles and larger strands of the left bundle-branch. There was extensive damage to the radiations of the left bundle-branch, with replacement fibrosis, in Cases 6, 7, and 8 (Fig. 5, 6, and 7); in Case 6 the left bundle-branch had undergone recent changes alongside older ones (Fig. 7), as a result of recurrent myocardial infarction. Acute probably reversible lesions, such as intra- and extracellular oedema (Fig. 8 and 9), cloudy swelling and vacuolization of myocardial cells with preserved myofibrils and

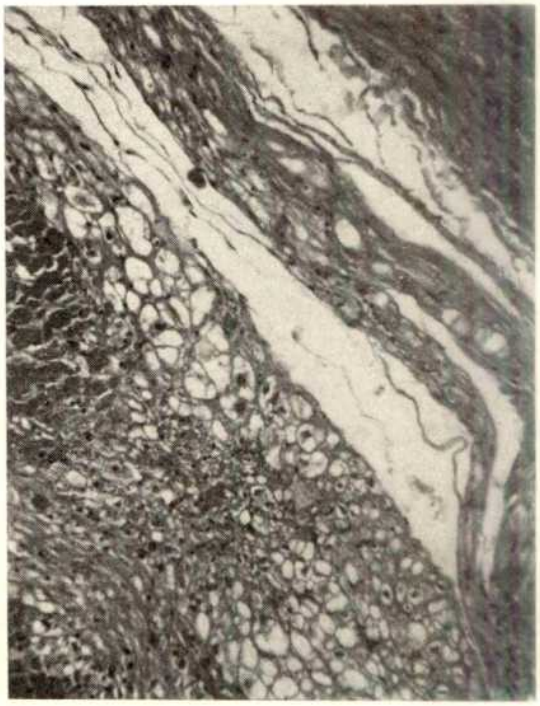

FIG. 3

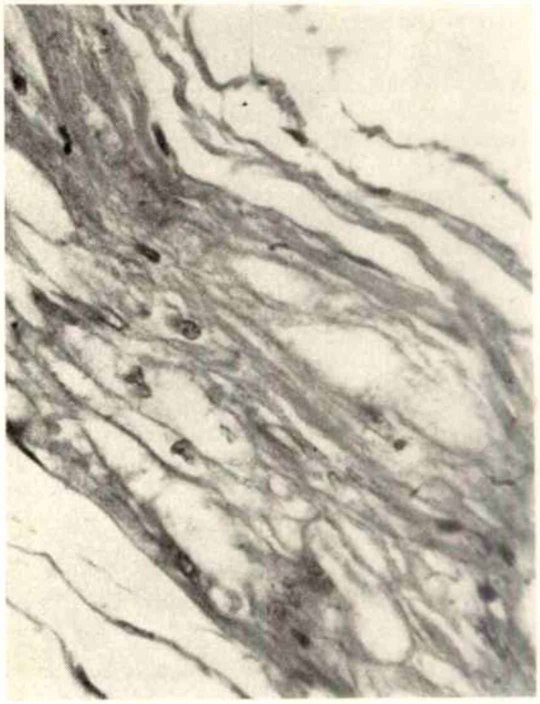

FIG. 4

FIG. 3 *Case 5. Gross vacuolization of the fibres of the left bundle-branch, adjacent to acute septal infarction. (H and E ×115.)*

FIG. 4 *Case 5. A detail of the severe vacuolization of the left bundle-branch fibres, with loss of myofibrils and of nuclei. (H and E ×450.)*

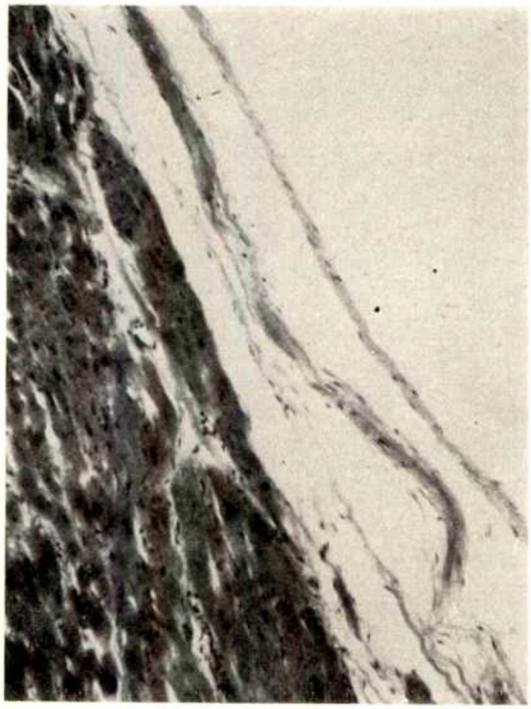

FIG. 5 *Case 7. Atrophy and fibrosis of individual fibres of the left bundle-branch, in patient with Marfan syndrome. (Azan ×115.)*

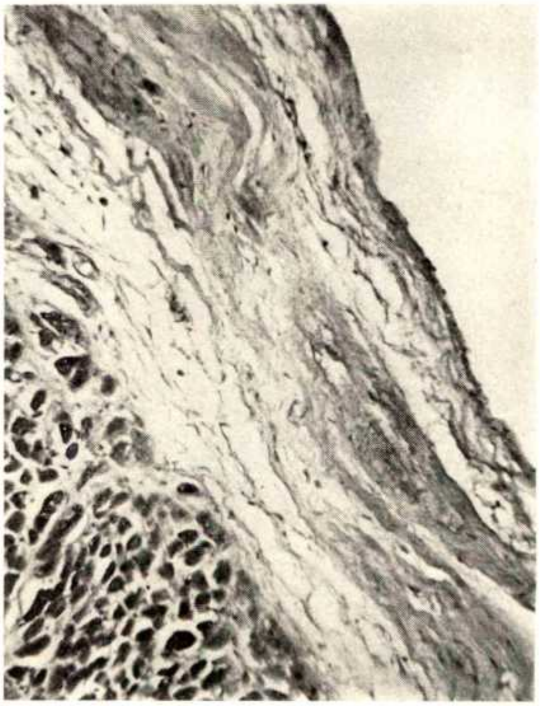

FIG. 6

nuclei (Fig. 10), leucocytic infiltration, and extravasation of erythrocytes throughout the left bundle-branch (Fig. 8, 9, and 10) were seen in 4 hearts (Cases 1 to 4).

In these cases the histological changes in the left bundle-branch were frequently less conspicuous and diffuse than in the adjacent myocardium, which showed extensive necrosis, with the usual accompanying changes of evolving myocardial infarction. This discrepancy is accounted for by a higher resistance of the conducting system than of unspecialized myocardium to ischaemic injury (Hackel *et al.*, 1972; Ekelund *et al.*, 1972). The left bundle-branch, owing to its subendocardial location and closeness to the cavity of the left ventricle, is also likely to be protected by transendocardial diffusion of oxygen.

FIG. 6 *Case 8. Advanced sclerotic replacement of the left bundle-branch, and myocardial fibrosis. (H and E ×115.)*

FIG. 7 *Case 6. A patch of subendocardial scarring from septal infarction, disrupting the left bundle-branch. (H and E ×115.)*

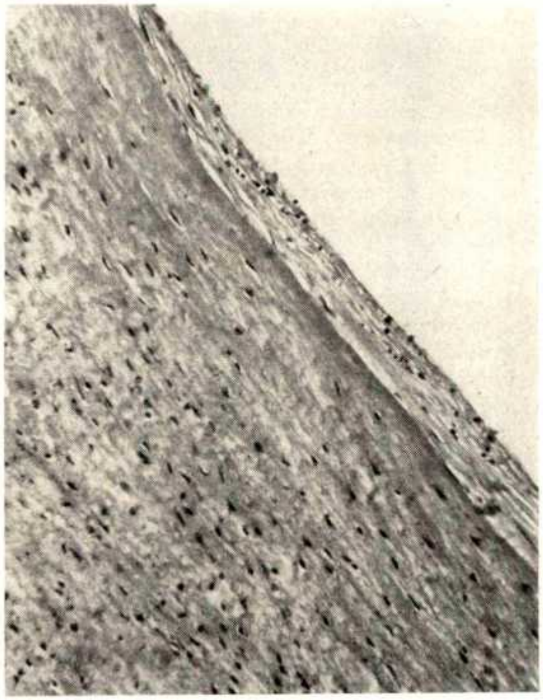

FIG. 7

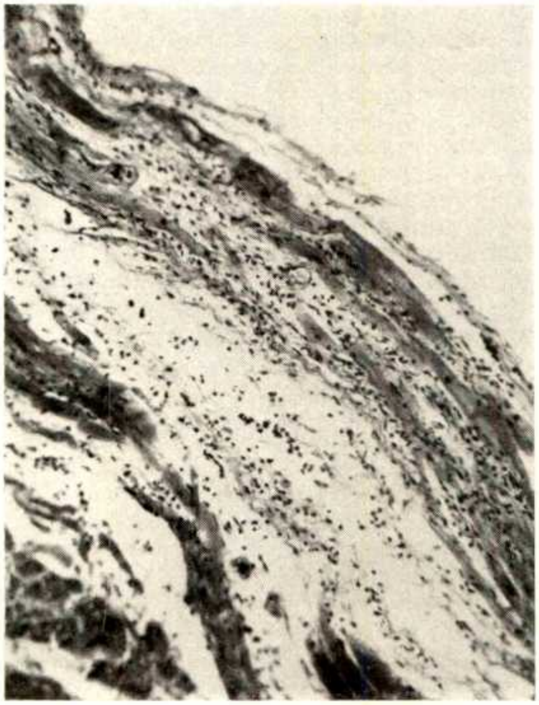

FIG. 8

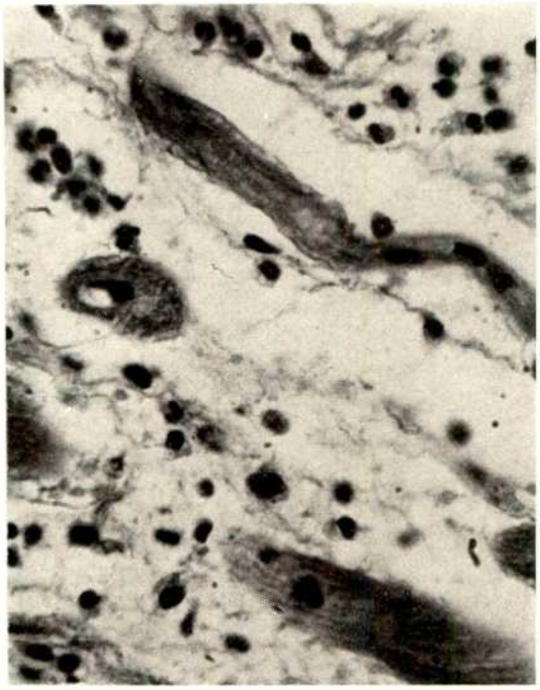

FIG. 9

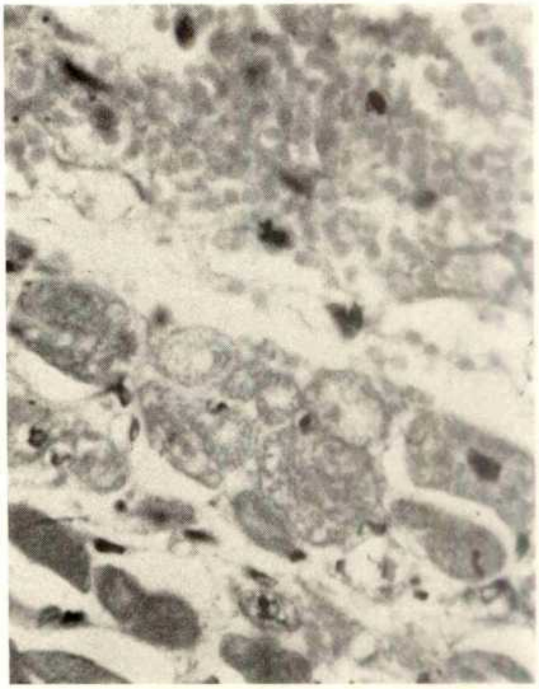

FIG. 10 *Case 3. Cloudy swelling and slight vacuolization of fibres of the left bundle-branch, with subendocardial haemorrhage, from acute septal infarction. (H and E ×450.)*

The location of the changes in the left bundle-branch have been illustrated diagrammatically in Fig. 11, in which the approximate site and the predominant type of lesion observed in each heart have been plotted, within a conventional sketch of a trifurcated left bundle-branch. This illustration, despite the intrinsic limitations of such a diagrammatic representation, may be helpful in portraying the salient morphological features in the present group of cases with 'left anterior hemiblock'.

## Discussion

Since attention has been drawn to the prognostic significance of hemiblocks complicating acute myocardial infarction (Atkins *et al.*, 1973; Lichstein, Gupta, and Chadda, 1975; Rizzon *et al.*, 1975),

FIG. 8 *Case 1. Subendocardial leucocytic infiltration and oedema, from acute septal infarction involving the left bundle-branch. (H and E ×115.)*

FIG. 9 *Case 1. Oedema and leucocytic infiltration of the left bundle-branch in myocardial infarction. (H and E ×450.)*

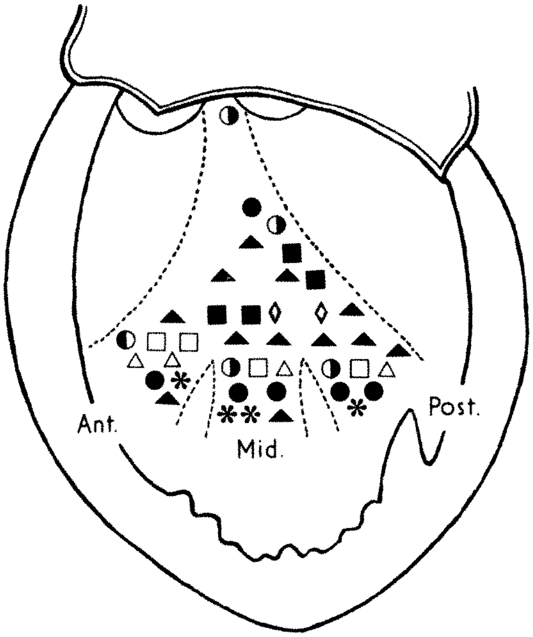

FIG. 11 *Diagrammatic illustration of the approximate incidence and distribution of changes in the left bundle-branch, in 8 cases of left anterior hemiblock. Within a conventional outline of the left bundle-branch, the lesions in individual cases are shown by a symbol, as follows: Case 1,* ◑*; Case 2,* □*; Case 3,* △*; Case 4,* ◇*; Case 5,* ●*; Case 6,* ✱*; Case 7,* ■*; Case 8,* ▲*. White symbols denote predominantly reversible changes, and black symbols predominantly irreversible changes (both in Case 1).*

serious difficulties have arisen concerning the interpretation of histological signs of damage to the conducting system, in relation to the pathogenesis of the conducting disorder. Rizzon *et al.* (1975) have recently stressed that anatomical disruption of the conducting pathway by manifestly irreversible lesions, the accepted basis for chronic heart block, including hemiblock (Demoulin and Kulbertus, 1972), is often not seen in cases of myocardial infarction. It has been shown that in the acute stage, the classical easily detected and well-defined 'interruption' of the conducting system is less often seen and less significant than probably reversible and sometimes mild changes, whose extent and functional significance are difficult to determine precisely. There is a need for a working hypothesis to relate histological to electrocardiographic changes. Block after infarction often disappears in patients surviving the early stage; these transient conduction disturbances may well be the result of the reversible changes described above, as well as of other factors (e.g. electrolyte balance, *p*H, parasympathetic reflexes, etc.) quoted by Hackel *et al.* (1972). However, Ekelund *et al.* (1972) observed that even relatively severe degeneration of the conducting tissue in myocardial infarction may be unassociated with conduction defects.

The overall impression from the evidence presented is that the concept of left anterior hemiblock is difficult to reconcile with the histological findings within the left bundle-branch in that the changes in the bundle-branch do not show any precise and distinctive pattern. Only in Cases 2 and 3 did the lesions in the anterior part of the left bundle-branch predominate; in the other 6 cases the damage to the left bundle-branch was widespread, affecting particularly the middle and posterior radiations. The origin of the left bundle-branch was seldom involved (Fig. 11). There were both acute and chronic changes affecting the left bundle-branch in all the hearts examined though these were variable in distribution, type, and severity. This implies that a diseased left bundle-branch is related to the electrocardiographic abnormality described as 'left anterior hemiblock'. This electrocardiographic pattern, however, was not always present nor invariably associated with histological injury confined to the anterior part of the left bundle-branch.

Coexisting cardiac lesions, within and outside the left bundle-branch, notably those involving the septal and parietal walls of the left ventricle, should also be considered in discussing the pathological counterpart of the electrocardiographic pattern which goes under the name of 'left anterior hemiblock' (J. Lenègre, 1971, personal communication).

These conclusions are based on an examination of hearts obtained from a group of patients most of whom had acute lesions, but are in agreement with those of Demoulin and Kulbertus (1972) who studied chronic cases of 'left anterior hemiblock'. It is opportune to make another plea for sounder clinicopathological assessment and proper terminology of the so-called hemiblocks.

I thank Professor P. Rizzon (University of Bari), Professor L. Matturri (University of Milan), and Dr. J. C. Demoulin (the University of Liège) for support.

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# Histopathological findings in two cases of *torsade de pointes* with conduction disturbances

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*Histological studies were made of the conducting system and the myocardium in two cases of* torsade de pointes *with complex disturbances of impulse conduction and formation. A fairly similar clinicopathological pattern was seen, consisting of an unusual association of non-interruptive, widespread damage to the conducting system with the intermittent and variable electrocardiographic disorders. The inherent desynchronization of cardiac action and the bilateral, uneven, and partial disruptions of the bundle-branches have been tentatively correlated, pathophysiologically, with the re-entry circuit, or mechanism, which is held to be responsible for the cyclic fluctuation of QRS axis, peculiar to* torsade de pointes.

*Torsade de pointes,* a form of life-threatening ventricular tachyarrhythmia in which the QRS polarity oscillates over runs of 3 to 20 beats, was recognized long ago (MacWilliam, 1923) and has been defined more recently by Dessertènne (1966, 1967). Yet, neither the peculiar nature of *torsade de pointes* nor its denomination is unanimously accepted.

Recently an authoritative editorial by Krikler and Curry (1976) carefully considered the semantic etymology, pathophysiological aspects, and clinical features of *torsade de pointes*; the conclusion was reached that it should be treated diagnostically as a separate arrhythmia, being an 'atypical ventricular tachycardia'. It is peculiar to this arrhythmia to be frequently associated with major disturbances in impulse formation and conduction, with bradycardia (Han *et al.,* 1966; Motte *et al.,* 1970).

The aetiological bases (see Krikler and Curry, 1976) encompass congenital defects (prolonged QT syndrome), acquired heart diseases (myocarditis, coronary atherosclerosis), myocardial infarction (rarely), Prinzmetal's variant angina, electrolytic disorders (hypokalaemia, hypomagnesaemia), and pharmacological overdose or side effects (diuretics, quinidine, lignocaine, amitryptiline and some other antidepressant drugs). From the pathophysiological standpoint the arrhythmia seems to be the result of unsynchronized cardiac activation (Han *et al.,* 1966) and/or impaired repolarization, favouring a particular re-entry pattern (Raynaud *et al.,* 1969; Evans *et al.,* 1976).

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The morphological basis of *torsade de pointes* is largely unknown: only a brief macroscopical annotation of moderate coronary atherosclerosis exists in one case (Benaim *et al.,* 1975), histological documentation of myocarditis in another (Somerville, 1975), and in a third case there is a vague record (Krikler and Curry, 1976).

While being aware of the limitations of clinicopathological information in relation to the mechanisms of ventricular tachyarrhythmias (Rossi, 1969), this lack of data seems to justify this histological study of the association of lesions of the conducting system with *torsade de pointes* in the present two cases.

## Subjects and methods

Two subjects who had developed *torsade de pointes* in the course of severe, intermittent, and varied disturbances in impulse conduction and formation were studied. Clinico-electrocardiographic and postmortem data were reviewed and correlated with a detailed study of the histological findings in the atrioventricular conducting system, to permit a reliable anatomoclinical comparison.

At necropsy a single block (besides different fragments for routine control studies) was cut away from each heart, encompassing the lower atrial and almost the entire ventricular septum, with the central fibrous body in between. This block, containing the node of Tawara with its atrial approaches, the common bundle and most of the bundle-branches was serially sectioned (every

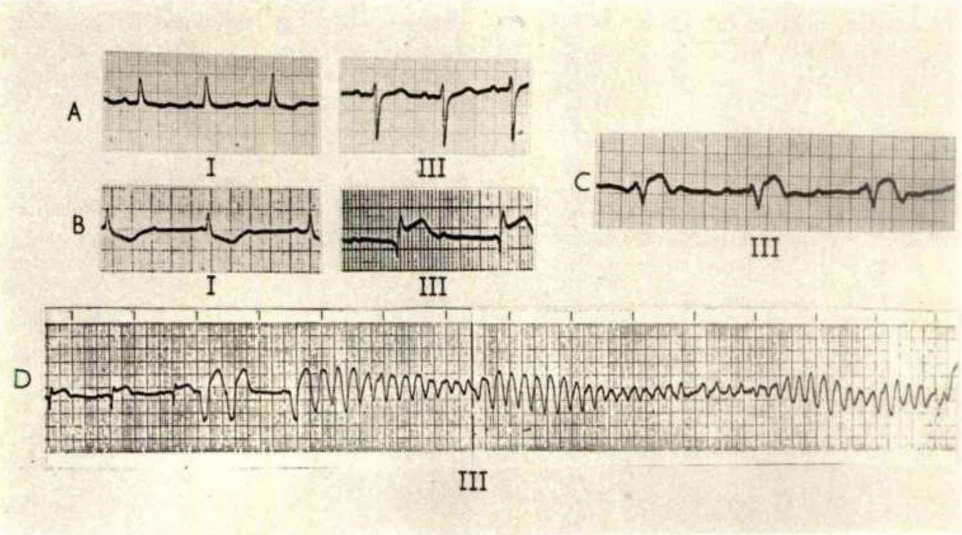

FIG. 1 *Electrocardiograms of Case 1. (A) Pronounced left axis deviation, receded one day later (B) with the onset of atrioventricular block with narrow QRS complexes. (C) Atrioventricular and intraventricular conduction disturbances during cardiac monitoring. (D) Prolonged PQ interval and a late extrasystole falling on the U wave, followed by bursts of* torsade de pointes.

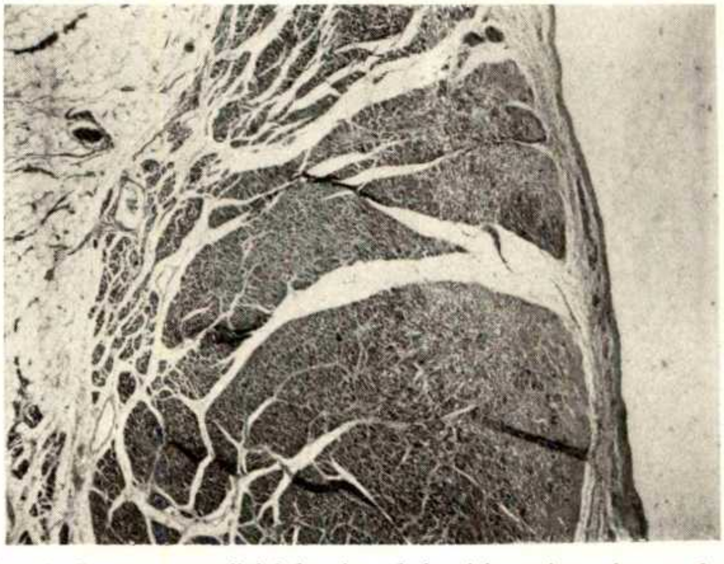

FIG. 2 *Case 1. Recent myocardial infarction of the right atrium, close to the approaches to the atrioventricular node. (H and E × 12.)*

150 μ) along the longitudinal plane of the septa and perpendicularly to their endocardial surfaces (see Rossi, 1969). The slides were stained with haematoxylin-Eosin (H and E) and, occasionally, with trichromic Azan.

## Case reports

### Case 1

A 55-year-old man was admitted to hospital, three days after he had suffered from severe praecordial pain, with the diagnosis of myocardial infarction. The first electrocardiogram showed evidence of acute myocardial infarction of the anterior wall, sinus tachycardia, and episodes of sinus arrhythmia. Three days later, during recurrence of episodes of praecordial pain, complete atrioventricular block (atrial rate 85 per minute and ventricular 48 per minute, with narrow QRS complexes) was recorded, with superimposed evidence of acute myocardial infarction of the posterior wall. The pronounced left axis deviation registered the day before was much reduced (Fig.

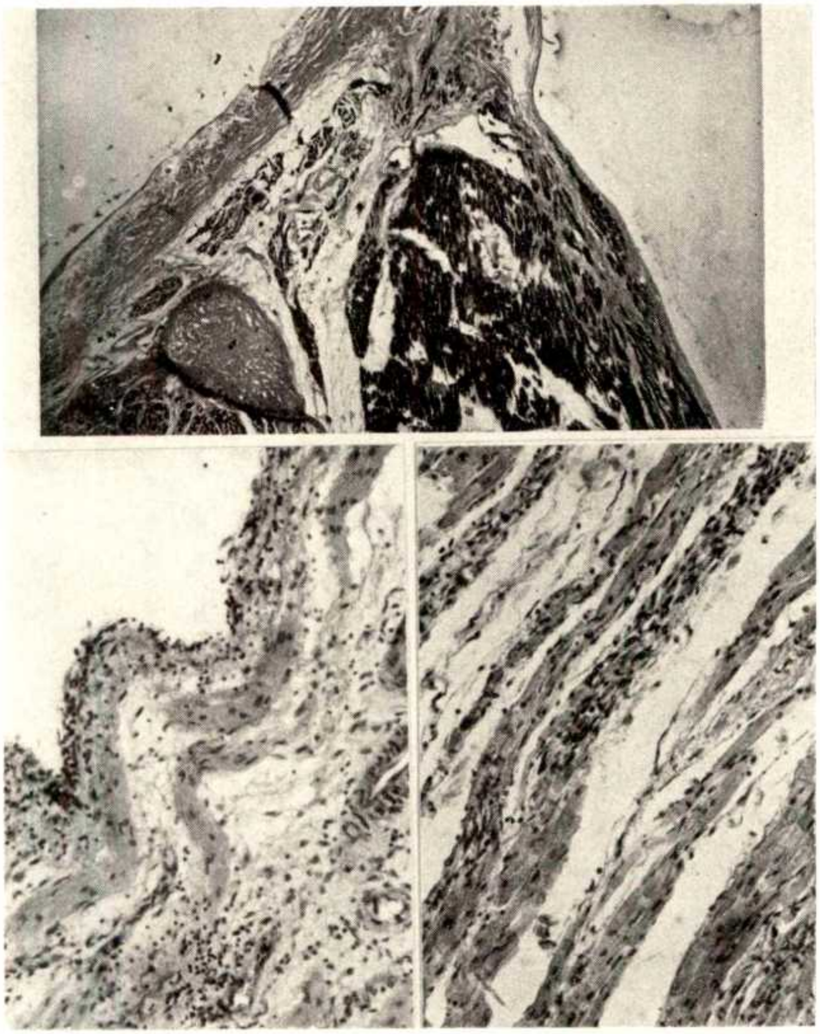

FIG. 3 *Case 1. Above: The atrophic bifurcation of the His bundle, on the left side of the septal summit, contains interstitial fat cells; the intramural root of the right bundle-branch is also shown. Below left: Fibres of the left bundle-branch involved in subendocardial oedema and leucocytic infiltration from adjacent acute myocardial infarction. Below right: The right bundle-branch, in its intramyocardial course, partially damaged by recent myocardial infarction. (Above: Azan × 22; Below: H and E × 115.)*

1 A, B). The following day the atrioventricular block underwent variations from complete to first-degree, and ventricular extrasystoles with attacks of ventricular fibrillation occurred. The patient was monitored and an endocardial electrode for demand pacing was inserted; the atrioventricular block continued to vary from second to first degree (ventricular rate 50 to 60 per minute). Direct current countershock was employed twice and lignocaine (100 mg) was twice injected intravenously, to stop life-threatening paroxysms of ventricular fibrillation. Ventricular extrasystoles and bursts of *torsade de pointes* were also recorded (Fig. 1 D); periods of atrial tachycardia were also recorded. The QRS complex occasionally widened (Fig. 1 C), becoming progressively aberrant, and the ventricular rate fell to 30 per minute until death occurred as the result of irreversible ventricular fibrillation.

At necropsy, cardiac hypertrophy, severe coronary atherosclerosis, and extensive, early myocardial infarction of the left ventricular walls and of the septum were found, and histologically confirmed.

The histological study of the conducting system showed a normal sinoatrial node, patchy areas of subacute atrial infarction (Fig. 2) close to the posterior approaches to a well-preserved atrioventricular node; the lower common bundle contained interstitial fat cells and the bifurcation was also very atrophic. The bifurcation (Fig. 3) was located on the left side of the ventricular septum and gave rise to a precociously intramural right bundle-branch, with a long intramyocardial course; the left bundle-branch had a normal configuration. The ventricular septum was packed with confluent areas of fresh and recent myocardial infarction, with necrosis and severe degeneration of fibres, extensive leucocytic infiltration and patchy haemorrhage, and early macrophagic and fibroblastic activity. The left bundle-branch was partially involved in changes around the margin of the infarct (subendocardial oedema, leucocytic infiltration, and haemorrhage—Fig. 3), whereas the right bundle-branch in its intramural course was directly and more seriously affected, though not totally interrupted, by changes of recent infarction (Fig. 3).

Summing up, the alterations of the posterior approaches to the atrioventricular node, the atrophy of the common bundle and the bilateral, though incomplete, disruption of the bundle-branches may account, anatomoclinically, for the electrocardiographic evidence of variable atrioventricular block with transient impairment of bundle-branch conduction (particularly right).

## Case 2

An 87-year-old man entered the hospital for cardiac failure and pulmonary tuberculosis. Electrocardiograms (monitoring periods included) showed atrial arrhythmias, incomplete (3:1) and occasionally complete (ventricular rate about 40 per minute), atrioventricular block, depressed ST segment and deep negative T waves, with prolongation of QT interval (0·60 s at a rate of 40 per min); ventricular extrasystoles and short bursts of *torsade de pointes* (Fig. 4 A) and of ventricular tachycardia and fibrillation occurred. During phases of complete atrioventricular block the QRS complexes were widened (patterns of right bundle-branch block type—Fig. 4 B). The patient died from syncope, 22 days after admission.

At necropsy, the heart was enlarged owing to dilatation and hypertrophy; the endocardium and valves were normal; the myocardium was brownish-yellow and the coronary arteries showed severe atherosclerosis. No relevant histological pictures, besides the confirmation of the foregoing changes, were seen.

The histological study of the conducting system showed fibrosis of the atrioventricular node (Fig. 5), degeneration and sclerosis of the common bundle; the bifurcation that was located on the right of the septal summit was partially affected on its left side, a large number of the fibres of the origin of the left

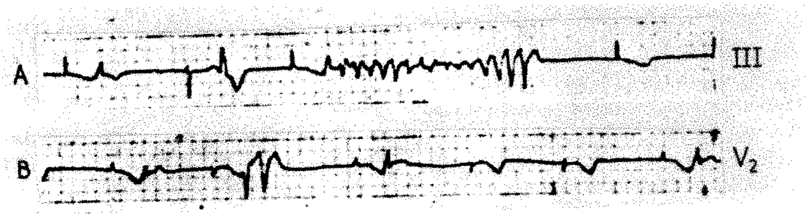

FIG. 4 *Electrocardiogram of Case 2. (A) Complete atrioventricular block with ventricular extrasystoles (R on T type); an extrasystole falls on the terminal T wave of the third QRS complex, initiating a short run of* torsade de pointes. *(B) Combined atrio- and intraventricular conduction disturbances, with ventricular extrasystoles.*

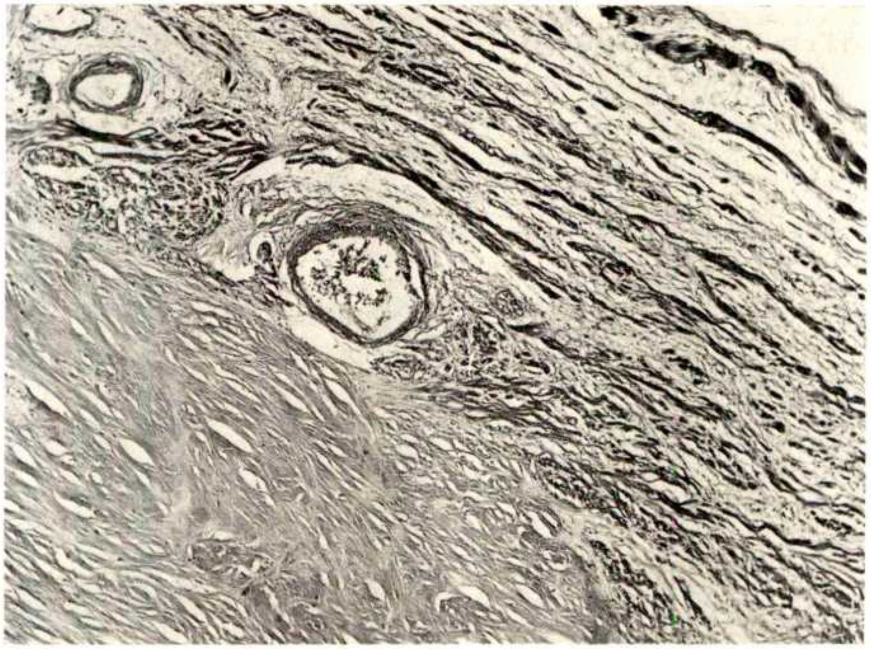

FIG. 5 *Case 2. Fibrosis of the atrioventricular node. (H and E ×25.)*

bundle-branch having undergone fine atrophy of the type seen in Lev-Lenègre's disease (Fig. 6). The upper subendocardial part of the right bundle-branch was, also, partially sclerotic (Fig. 6). Patchy myocardial fibrosis and diffuse brown atrophy were seen in the ventricular septum and elsewhere in the heart.

From the clinicopathological standpoint, the presence of a partially fibrotic atrioventricular node and common bundle, with severe but incomplete sclerosis of both bundle-branches, may be correlated with the atrioventricular and bundle-branch conduction disturbances registered in the electrocardiograms.

## Discussion

The present two cases, notwithstanding obvious differences in the nature and type of the basic disease and related changes, seem to have a common pattern as regards the disturbances in impulse conduction and formation on the one hand and the topography and degree of conducting system lesions on the other. In both of them, *torsade de pointes* occurred against a background of intermittent atrioventricular block of varying degree, associated with transient impairment of bundle-branch conduction and with bursts of ventricular extrasystoles and fibrillation.

The underlying histopathological changes, mostly acute in Case 1 and chronic in Case 2, affected fairly similar tracts of the conducting system, namely the region of the atrioventricular node, the common bundle, and, more particularly, both bundle-branches, without producing a complete disruption of the conducting pathway at any point.

Overall, the disturbances of atrioventricular and intraventricular conduction can be accounted for by the histological findings, but the variable and transient character of the electrocardiographic disorders indicates the likely association of functional factors, which escape precise explanation. The disturbances in atrioventricular impulse transmission should be ascribed mostly to the lesions of the undivided as well as of the branching portions of the conducting system, whereas the impairment in intraventricular conduction and, possibly, the shift of cardiac axis (in Case 1) were, more probably, dependent upon the bilateral bundle-branch injuries.

Lesions of this kind are far from rare in the pathology of heart block, including the so-called tri- and bifascicular blocks (Rosenbaum, 1970). In the present cases, however, such changes interfered, intermittently in a complex way, with impulse conduction and formation, favouring the development of *torsade de pointes;* clinicopathologically this is an uncommon occurrence.

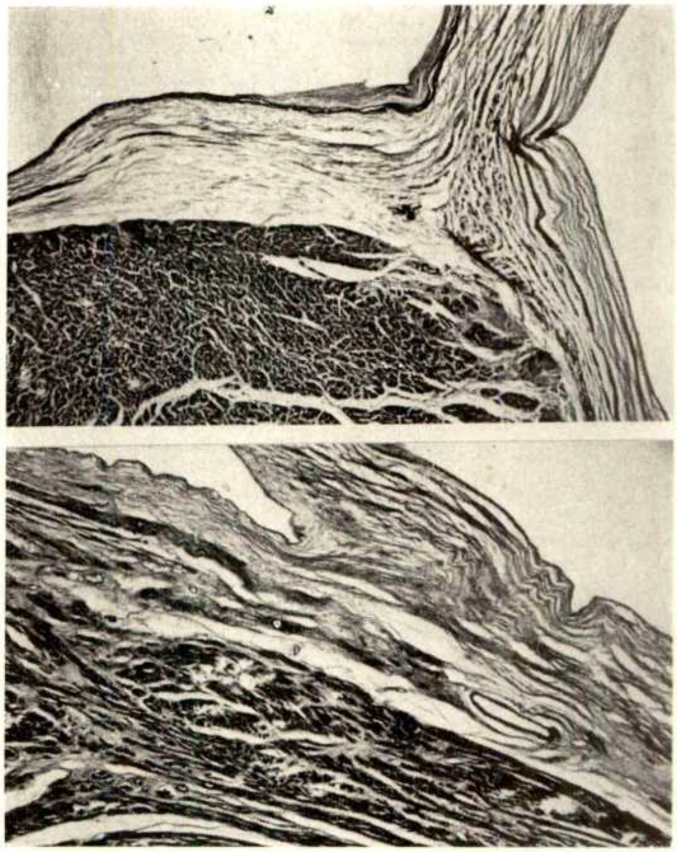

FIG. 6 *Case 2. Above : The bifurcation of the His bundle on the right side of the septal summit, with diffuse atrophy of the origin of the left bundle-branch. Below : The partially sclerotic right bundle branch, in its upper subendocardial course. (H and E × 22.)*

Electrophysiological considerations suggest that *torsade de pointes* occurring in patients with diseased conduction and/or disordered synchronism of the heart beat does not represent chaotic cardiac action from enhanced ectopic (focal) activity, but rather a well-organized electrical process of ventricular re-entry (Dessertènne, 1973; Krikler, Curry, and Evans, 1976), the peculiar layout and pattern of which produce cyclic oscillations of QRS polarity. These pathophysiological considerations suggest, therefore, that a selective histological investigation of the conducting system would be indicated rather than a search for pathological 'foci' somewhere in the heart. Indeed, lesions of the conducting system are not only credited with enhancing cardiac desynchronization in general, but the lesions of the bundle-branches, the left in particular, are held to have a precise bearing on shifts of QRS axis (Watt, Murao, and Pruitt, 1965; Rosenbaum, 1970).

The present histopathological findings are in keeping with this argument and are consistent, to some extent, with current views of the electrophysiology of *torsade de pointes,* suggesting tentatively anatomofunctional correlation. In these two cases, the multiple lesions of the conducting pathways could have been responsible for conduction blocks with desynchronization, underlying the ventricular tachycardia, while the bilateral incomplete disruptions of the bundle-branches were providing the specific histological basis for the 'coiling' of the QRS axis.

Accordingly, one may postulate that, sometimes, in the presence of heart block and under, so-far, unclear conditions, the affected branches of the conducting system (or the preserved parts of them) may happen to provide the specific re-entry circuit and/or mechanism of *torsade de pointes,* characterized by periodic twists of the cardiac electrical axis.

Changes of this type, location, and degree, apparently critical to the pathogenesis of *torsade de pointes*, are not likely to occur in many patients with heart blocks; which, in turn, could explain why only a few, among all the cases of conduction disturbances, are seen to develop this arrhythmia.

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# Closure of pericardium after open heart surgery
## *A way to prevent postoperative cardiac tamponade*

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*Between July 1968 and December 1975, 821 patients underwent open heart operations. In 596 cases the pericardium was left open and in 225 the pericardium was closed. Forty-one patients in the open pericardium group required reoperation and 23 of these had tamponade. Four patients in the closed pericardium group had reoperation but there was not a single case of tamponade. In most cases that required reoperation the bleeding was from extrapericardial sources. Absence of tamponade in the closed pericardium group can be explained by the fact that blood from extrapericardial sources of bleeding cannot collect round the heart because the pericardium is closed. Thus closure of pericardium helps to prevent tamponade.*

*Reoperations some months or years after the original operation are technically easier and less hazardous if the pericardium has been closed because the closed pericardium prevents the heart from becoming adherent to the back of sternum and also because there are fewer adhesions in the pericardial cavity.*

Cardiac tamponade is a serious complication after open heart surgery and much attention has been paid to this problem in the past decade or so. The usual practice has been to leave the pericardium widely open in communication with one of the pleural cavities, so that blood from the pericardial sac and the mediastinum could drain into the pleural cavity. This practice of leaving the pericardium open has not decreased the incidence of postoperative cardiac tamponade. We find that by closing the pericardium after open heart surgery the incidence of postoperative tamponade can be drastically reduced if not completely eliminated. In recent years another great disadvantage of leaving the pericardium open has come to light. This is evident when such a patient requires reoperation some months or years after the original operation. Reoperation is technically more difficult because of adhesions. The right ventricle and the aorta become adherent to the back of the sternum and while reopening a previous sternotomy the right ventricle or the aorta may be inadvertently entered causing fatal haemorrhage. A closed pericardium will prevent the aorta and the right ventricle from adhering to the sternum. A closed pericardial cavity is also clean and consequently adhesion formation is much less.

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## Subjects and methods

Between July 1968 and December 1975 a total of 821 patients underwent open heart operation in Hong Kong University Surgical Unit. The age of the patients ranged from 8½ months to 61 years. There were 527 cases of congenital heart disease and 278 cases of acquired heart disease (Table 1). In 596 (72·6%) cases the pericardium was left wide open and in 225 (27·4%) cases the pericardium was closed.

TABLE 1 *Types of original operation*

| *Operation* | *No.* | *One reoperation* | *Second reoperation* |
|---|---|---|---|
| Tetralogy of Fallot | 194 | 20 | 1 |
| Atrial septal defect | 143 | 6 | 2 |
| Ventricular septal defect | 120 | 5 | |
| Pulmonary stenosis | 36 | 1 | |
| ASD and PS | 29 | 2 | |
| ASD and VSD | 5 | 1 | 1 |
| Mitral valve replacement | 148 | 1 | |
| Double valve replacement | 47 | 5 | 1 |
| Aortic valve replacement | 36 | 3 | |
| Open valvotomy (aortic and mitral) | 47 | 1 | |
| Others | 16 | | |
| Total | 821 | 45 | 5 |

### Operative technique

In all cases the chest was opened through a vertical sternotomy avoiding the pleural spaces as and when possible. The anterior part of the pericardium was opened from the level of the left innominate vein to the diaphragm, with an extension of the incision to the left along the diaphragm for a short distance. This makes it easier to lift the heart for insertion of the left ventricular vent. The thymus and the fat in the upper mediastinum were carefully dissected. The edges of the pericardium were lifted to the level of the sternum with the aid of three stay sutures on each side and the sternal spreader was applied inside the pericardial edges. This lifts the heart up and also probably prevents the pericardium from shrinking (Cunningham *et al.*, 1975). At the end of operation heparin was neutralized with protamine and an intravenous injection of epsilon aminocaproic acid (EACA) was given. All cardiac incisions and sites of aortic cannulation and aortotomy were carefully checked for adequate haemostatis.

**(a) Closed pericardium group** The pericardium was closed with interrupted silk sutures inserted about 1·5 cm apart, leaving the lower inch of the pericardium open. Two drains were then inserted in the mediastinum, an upper reaching the level of the back of the manubrium sterni and a lower lying behind the lower part of the body of the sternum. Mayon plastic surgical tubing was used for drainage (internal diameter 0·9 cm for adults, and 0·6 cm for children). No drain was inserted inside the pericardial cavity; our experience showed that this was not necessary, as the lower mediastinal tube drains the pericardial cavity adequately. If the pleura was inadvertently opened, it was sutured after thorough suction of the pleural cavity and the top end of the upper mediastinal drain was left in the upper pleura instead of behind the manubrium sterni.

**(b) Open pericardium group** In these patients the pericardium was not sutured and the right pleura was left open in communication with the pericardial cavity; one mediastinal and one pleural drain was used.

TABLE 2 *Cases requiring reoperation*

| *Pericardium* | *No.* | *No. of cases with tamponade* |
|---|---|---|
| Open 596 (72·59%) | 41 (6·87%) | 23 (3·85%) |
| Closed 225 | 4 (1·77%) | 0 |
| Congenital 154 | | |
| Acquired 71 | | |
| Total 821 | 45 (5·48%) | 23 |

Vacuum suction (10 to 15 cm water) was applied to the drains separately in the intensive care unit. In addition the drains were milked every few minutes.

TABLE 3 *Indications for reoperation*

| *Indication* | *No.* | *Pericardium* |
|---|---|---|
| Cardiac tamponade | 23 | Open |
| Excessive blood loss | 18 | Open |
| Persistent bleeding | 4 | Closed |

### Results

Forty-five (5·5%) of the total of 821 cases required reoperation for bleeding or tamponade or both; 41 of these cases were in the open pericardium group and 5 of these required second reoperation; only 4 cases in the closed pericardium group required reoperation. In the open pericardium group, 23 patients showed evidence of cardiac tamponade. In contrast to this there was not a single case of cardiac tamponade in the group of patients in whom the pericardium was closed (Table 2).

**Indications for reoperation (Tables 3 and 4)**

**Cardiac tamponade** Twenty-three patients were reopened with a diagnosis of cardiac tamponade and this was confirmed at operation. All these cases were in the open pericardium group. All but one case developed tamponade in the early postoperative period. There was only one case of delayed tamponade in the series (Table 4) and this was related to anticoagulant therapy. The clinical picture of tamponade was one of 'low output failure' with pale cold extremities, falling blood pressure, tachycardia, rising central venous pressure, and a fall in urine output. The decrease in urine output was a very valuable sign and appeared early. There was no case of cardiac tamponade among patients in whom the pericardium was closed.

**Continued excessive bleeding** Eighteen patients were reopened because of continued excessive blood loss and in all these the pericardium was left wide

TABLE 4 *Time of reoperation*

| *Pericardium* | *2–6 h* | *7–12 h* | *13–24 h* | *25–48 h* | *72 h* | *1 wk* |
|---|---|---|---|---|---|---|
| Open | 9 | 13 | 7 | 10 | 6 | 1 |
| Closed | | | | 3 | 1 | |

TABLE 5 *Amount of drainage in reoperated patients*

| *Pericardium* | *Total volume to time of reoperation (mean)* | *Amount per hour (average)* |
|---|---|---|
| Open | 1225 ml | 224 ml |
| Closed | 850 ml | 36 ml |

open. The average blood loss in these patients was 224 ml per hour. The details of the amount of drainage are given in Table 5.

**Persistent bleeding** Four patients required reoperation for persistent bleeding but the amount of drainage was not excessive and all of them were in the closed pericardium group. At operation little or no blood could be found in the pericardial cavity. In one case there was bleeding from the entry site of the upper mediastinal drain and in the others there was bleeding around the sternal wires and the thymus.

### Amount of drainage (Table 5)

The comparison of the amount of drainage in the two groups requiring reoperation is given in Table 5. The amount of drainage was much greater in the open pericardium group than in the closed pericardium group.

### Source of bleeding at reoperation (Table 6)

The common sites of bleeding were in the anterior mediastinum where there may be numerous small oozing points. One frequent source of bleeding was the back of the sternum where the self-retaining sternal spreader lay in contact with it; the spreader stripped the pleura and other soft tissues including the periosteum from the back of the sternum and the costal cartilages. The cases with bleeding from the cardiac incisions or the aorta were mostly encountered earlier in the series.

TABLE 6 *Source of bleeding at reoperation*

| *Source* | *No.* |
|---|---|
| Extrapericardial | |
| Mediastinal pleura, sternum, thymus, pericardium, drain sites | 32 (71·11%) |
| Intrapericardial | |
| Atrial incisions, right ventriculotomy, aortic incisions | 9 (20%) |
| No definite source | 4 (8·88%) |

TABLE 7 *Results of reoperation*

| | *Pericardium* | *No.* |
|---|---|---|
| Mortality | Open | 8 (17·77%) |
| | Closed | 0 |
| Tracheostomy | Open | 10 (22·22%) |
| | Closed | 0 |
| Wound infection | Open | 4 (8·88%) |
| | Closed | 1 |

### Results of reoperation (Table 7)

Eight (17·8%) patients died between 1 and 3 weeks after operation, but in none was death directly related to reoperation. No patient in the closed pericardium group died after reoperation. Ten patients required tracheostomy and were in the open pericardium group. There were cases of wound infection after reoperation in both groups. Craddock, Logan, and Fadali (1968) reported a death rate of 36 per cent in those requiring reoperation, and in the series of Nelson, Jenson, and Smoot (1969) the mortality was 7 per cent.

## Discussion

In this series of 821 cases, 23 patients developed postoperative cardiac tamponade. This is an incidence of 2·8 per cent and compares favourably with the results of Craddock *et al.* (1968) and Nelson *et al.* (1969), who reported incidences of 5·7 and 3·4 per cent, respectively. Cardiac tamponade is a surgical emergency and the outcome depends on early diagnosis and quick decompression. The diagnosis of postoperative cardiac tamponade is often delayed because of the difficulty of differentiating it from other causes of low cardiac output, especially in the absence of reliable radiological signs. The use of 'juxtaposed epicardial-pericardial clips' (Meckstroth and Cattaneo, 1974) in diagnosing postoperative tamponade is of limited value. We found it difficult to obtain standard positions for the clips for all patients; in addition their position tends to vary with phases of respiration and with cardiac systole and diastole. Furthermore, erosion of the metal clip into the heart remains a potential danger. Measurement of pericardial or mediastinal pressure to diagnose tamponade (Frater, 1970) also has its limitations. The best solution, therefore, appears to be not to allow postoperative cardiac tamponade to develop at all; closure of the pericardium after open heart surgery seems to be able to achieve this. This becomes evident from comparison of the two groups in our series. There was no incidence of tamponade in the 225 cases in whom the pericardium was closed, as opposed to 23 cases of tamponade in the 596 cases in whom the pericardium was left wide open in communication with the right pleural cavity. Cunningham *et al.* (1975) have recently reported a similar experience. In their series of 100 cases in whom the pericardium was closed after open heart surgery there was not a single case of cardiac tamponade. As shown in Table 6, in most cases the postoperative bleeding occurred from extrapericardial sources. This was also the experience of others (Bentall *et al.*, 1964; Craddock *et al.*, 1968; Nelson *et al.*, 1969; Cunningham *et al.*, 1975). In most reported series haemopericardium was the cause of tamponade and in all of these patients the pericardium was left wide open. Blood from extrapericardial sources collects around the heart, and while most of it drains out some invariably clots causing tamponade. This has also been the cause of left atrial tamponade (Yacoub, Cleland, and Deal, 1966), and delayed tamponade (Nelson *et al.*, 1969; Ellison and Kirsh, 1974). The anterior surface of the closed pericardium acts as a collecting receptacle, where blood from the extrapericardial sources of bleeding collects and is immediately drained through mediastinal drainage tubes, thus preventing the collection of blood around the heart. After decannulation and neutralization of heparin and while carrying out haemostatis, blood quickly collects in the pericardial sac. After this has been removed by suction, there is rarely any bleeding from any of the cardiac or aortic sites; the blood usually gravitates from the back of the sternum, the mediastinal pleura, or the pericardium. This to a lesser degree may continue even after careful haemostatis and closure of the sternum. For several hours after open heart surgery the patients lie supine, and with the pericardium open blood will collect in the posterior part of the pericardial sac; before all can be drained out by suction some will no doubt clot. This seems the probable explanation for the high incidence of postoperative tamponade in the open pericardium group in this series and others (Craddock *et al.*, 1968; Hill *et al.*, 1969; Nelson *et al.*, 1969; Engelman *et al.*, 1970). In cases with open pericardium who required reoperation for continued excessive bleeding we found clots around the heart. Similar experience was also reported by others (Craddock *et al.*, 1968; Hill *et al.*, 1969; Engelman *et al.*, 1970). Surprisingly no blood was found in the pericardial cavity of the patients in the closed pericardium group who required reoperation for persistent bleeding. Cunningham *et al.* (1975) reported a similar experience in a group of 100 patients, 5 of whom required reoperation for excessive blood loss (2 litres or more). Therefore, it appears that postoperative cardiac tamponade can be prevented by closure of the pericardium after open heart surgery. This theory is completely opposed to the usual practice of leaving the pericardium wide open in the attempt to avoid tamponade. Before closing the pericardium, it is important to make absolutely certain that none of the cardiac or aortic wounds is bleeding.

There are other advantages in closing the pericardium. For example, the right ventricle is protected from any damage by the sharp posterior edge of the split sternum during closed heart massage in the postoperative period, especially in patients with dextrocardia. Another advantage of closing the pericardium is apparent in cases that require reoperation some months or years later. As we have shown, when the pericardium is closed after open heart surgery the pericardial cavity is fairly clean. Because of this adhesion formation is much less in these cases. This is well supported by the experimental work of Cliff, Grobety, and Ryan (1973). Their conclusion was that dense adhesions form when blood collects in the injured pericardium as so often happens in patients in whom the pericardium is left open after open heart surgery. Repeat operations may be required in certain patients for a variety of reasons some months or years after the original operation and are technically more difficult when adhesions are present. The right ventricle and the aorta may become adherent to the back of the sternum, and while a previous sternotomy is being reopened the right ventricle or aorta may rupture (Hylen *et al.*, 1970). Reoperation would be technically easier and less hazardous if the pericardium had been closed, because the heart is then not adherent to the back of the sternum and there are fewer adhesions in the pericardial cavity.

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# Non-invasive assessment of left ventricular function after correction of severe aortic regurgitation

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*Twenty patients were studied with simultaneous left ventricular cavity echocardiograms and apex cardiograms during the first two weeks after correction of severe aortic regurgitation. Endocardial echoes and apex cardiograms were digitized, so that left ventricular dimensions, their rates of change, and echo dimension-apex cardiogram relations could be studied. After aortic valve replacement, there was an early reduction in end-diastolic dimension, within 2 days, from 7·0±0·8 cm to 5·7±1·0 cm ($P<0·001$), while peak normalized shortening rate (peak $V_{cf}$) dropped from 1·9±0·6 to 1·4±0·6 $s^{-1}$ ($P<0·01$), and remained unchanged for the remainder of the study. Immediately after operation, striking abnormalities of isovolumic contraction and, to a lesser extent, of early relaxation, could be seen, which regressed over 4 to 7 days, except in 2 patients who developed a low output state. These changes in left ventricular dimension, $V_{cf}$, and isovolumic contraction could not have been described by any single 'measure' of left ventricular function.*

Although correction of aortic regurgitation can now be undertaken with low mortality, using either homograft or mechanical prostheses, there is still doubt as to the extent to which left ventricular disorder persists after operation. In order to study this question, several approaches have been used, including measurement of haemodynamic variables in the immediate postoperative period (Carey and Plested, 1972; Uhrenholdt *et al.*, 1973), formal postoperative cardiac catheterization and angiography (Gault *et al.*, 1970), measurement of systolic time intervals (Seabra-Gomez, Sutton, and Parker, 1974), cineangiographic observations of the movement of epicardial clips (McDonald, 1972), and echocardiographic assessment of left ventricular transverse dimensions (Burggraf and Craige, 1975). In spite of these studies, however, the nature of the left ventricular disorder remains uncertain, and there is little knowledge of sequential changes in individual patients, particularly in the immediate postoperative period. The present investigation, based on echocardiography, was designed to provide information about cavity dimensions, peak rates of wall movement, and contraction pattern in the period immediately after operation in a group of patients undergoing aortic valve replacement for free aortic regurgitation.

## Patients and methods

Twenty patients were studied, 15 men and 5 women, age range 18 to 61, average 35·8 years. All of them required aortic valve replacement for severe aortic regurgitation; though 4 had additional mitral valve replacement and 1 mitral valve repair, the dominant lesion in all was aortic. Clinical and operative data are given in Table 1.

Simultaneous echocardiograms and apex cardiograms were recorded in the immediate postoperative period. In 12 patients, a single examination was performed a mean of 7 days after operation, and in 8 multiple examinations were made, the earliest at a mean of 2 days and the latest 9 days after valve replacement. Echocardiograms were recorded with a Smith Kline Ekoline 20 ultrasonoscope connected to either a Cambridge or a Honeywell 1856 strip-chart recorder, using a 2·25 MHz 1·25 cm transducer. Clear continuous echoes of the endocardium of the left side of the septum and the posterior wall were obtained. Apex cardiograms were recorded with a Cambridge Scientific Instruments transducer with a time constant of 4 sec and a lower frequency limit of 0·04 Hz. All recordings were made photo-

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TABLE 1 *Clinical details*

| *Case No.* | *Age (y)* | *Sex* | *Aetiology* | *Additional* | *Bypass (min)* | *Hypothermia (°C)* | *Coronary perfusion* |
|---|---|---|---|---|---|---|---|
| 1 | 29 | M | Cong | Coarctn | 75 | 34 | R+L |
| 2 | 40 | F | Rh | — | 90 | 26 | — |
| 3 | 40 | M | ? | — | 133 | 30 | R+L |
| 4 | 32 | M | Cong | — | 60 | 34 | R+L |
| 5 | 39 | M | Rh | — | 105 | 34 | R+L |
| 6 | 61 | M | Rh | MVR | 95 | 30 | R+L |
| 7 | 29 | F | Rh | — | 55 | 34 | R+L |
| 8 | 50 | F | Rh | — | 95 | 30 | R+L |
| 9 | 30 | M | ? | — | 80 | 33 | R+L |
| 10 | 52 | F | Rh | — | 66 | 32 | R+L |
| 11 | 21 | M | Rh | — | 60 | 20 | — |
| 12 | 48 | M | Rh | — | 94 | 30 | R+L |
| 13 | 33 | M | ? | — | 74 | 33 | — |
| 14 | 19 | M | ? | — | 95 | 20 | — |
| 15 | 36 | M | Rh | — | 66 | 32 | R+L |
| 16 | 35 | M | Rh | MVR | 126 | 32 | — |
| 17 | 23 | M | Rh | MVR | 197 | 34 | R+L |
| 18 | 18 | M | Rh | MVR | 120 | 30 | R+L |
| 19 | 54 | M | Cong | — | 114 | 30 | R+L |
| 20 | 28 | F | Cong | — | 70 | 34 | R+L |

*Abbreviations:* Cong, congenital bicuspid valve; Rh, rheumatic; R+L, right and left coronary perfusion; MVR, mitral valve replacement.

graphically at a paper speed of 100 mm/s, and a simultaneous electrocardiogram was obtained (Fig. 1).

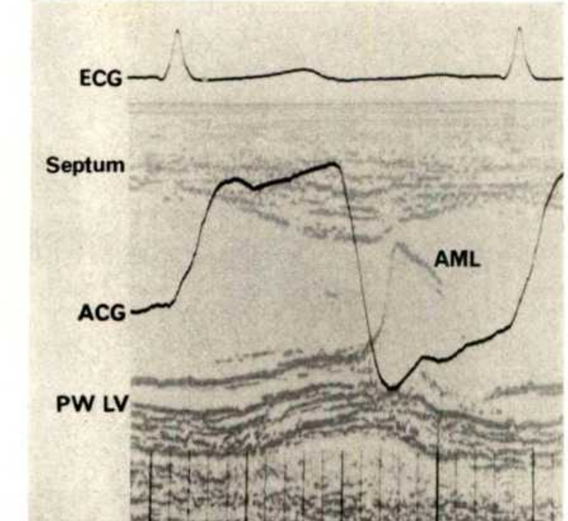

FIG. 1 *Simultaneous apex and echocardiograms from a patient with aortic regurgitation. PW = posterior left ventricular wall endocardium, AML = anterior mitral valve leaflet.*

## Digitization

Echocardiograms and apex cardiograms were digitized as previously described (Gibson and Brown, 1973), using a Summagraphics digitizer and a Prime 300 computer system. Data points were generated for the endocardium of the septum and posterior wall and for the apex cardiogram, together with calibration points defining a time interval of 0·5 s, 1 cm depth and two successive Q waves on the electrocardiogram spanning the beat to be studied. From this information, 129 interpolated data points were derived, and the information stored for subsequent calculations. Using an incremental plotter, plots were made of left ventricular dimension, its rate of change, expressed both in cm/s and in normalized form, and an apex cardiogram-echo dimension loop (Fig. 2).

Since the apex cardiogram is closely related to the left ventricular pressure pulse in time (Manolas *et al.,* 1975; Venco, Gibson, and Brown, unpublished), the interval from the onset of the upstroke to the 'E' point represents the period of isovolumic contraction. Normally, either no change or a small decrease (mean 6·2 ± 4·9%) in dimension occurs during this period: a larger decrease or outward wall movement thus represents an abnormal isovolumic shape change. Early relaxation was studied in a similar manner, and was taken as the interval between the 'knee' of the apex cardiogram occurring at the end of ejection and the 'O' point. Previous studies have shown the knee to correspond to the onset of the closing movement of

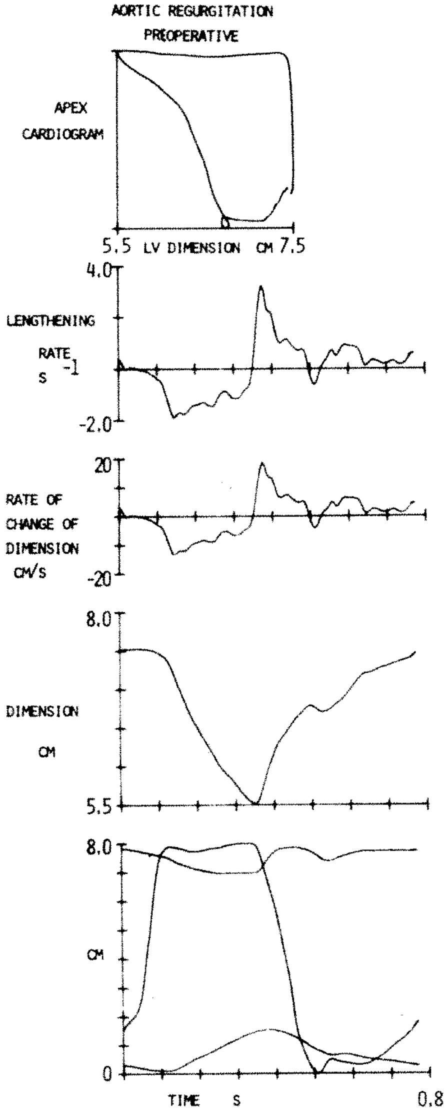

FIG. 2 *Computer output of preoperative record of Case 9. The lowest trace represents the digitized apex and echocardiograms, and above are plots of left ventricular dimension (D), rate of change of dimension (dD/dt), normalized rate of change of dimension (1/D.dD/dt), and the echo dimension-apex cardiogram loop. Outward movement of the left ventricular walls during the downstroke of the apex cardiogram is apparent.*

the aortic valve cusps and the 'O' point to be synchronous with the timing of peak rate of outward wall movement, thus following mitral valve opening by a short interval. Normally, 21 ±6·8 per cent of total diastolic excursion of wall movement occurs during this period. In order to quantify changes occurring during the periods of isovolumic contraction and early relaxation, the corresponding areas of the apex dimension loop were also measured. The loop itself was displayed on a Tektronix 4010 VDU using GINO-F display programmes, and the point corresponding to the onset of the upstroke, the 'E' point, the 'knee', and the 'O' point were identified with a cursor (Fig. 3). The two areas thus defined, together with that of the loop, were calculated by numerical integration, and normalized to a total value of 100 per cent.

End-diastolic dimension was taken as that synchronous with the QRS complex of the electrocardiogram, and end-systolic dimension as the minimum of the left ventricular dimension curve. Peak systolic and diastolic rates of wall movement were estimated in cm/s and normalized form. From the apex dimension loop, the extent of inward or outward movement during the upstroke or downstroke of the apex cardiogram were measured directly, and the corresponding areas were defined as described above, and expressed as a percentage of the total.

## Results

The results are given in detail in Tables 2 to 4.

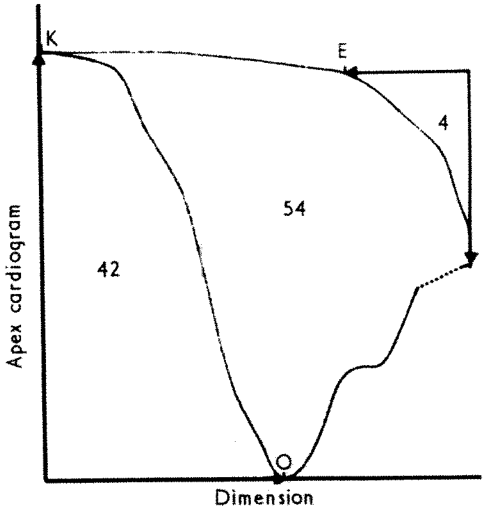

FIG. 3 *Echo dimension-apex cardiogram loop showing measurements of area, expressed as a percentage of the whole. The E point (E), 'Knee' (K), and 'O' point (O) are indicated.*

TABLE 2 *Changes in LV dimension*

| *Case No.* | *End-diastolic dimension (cm)* | | | | *End-systolic dimension (cm)* | | | | *Peak shortening rate ($s^{-1}$)* | | | | *Peak lengthening rate ($s^{-1}$)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* |
| 1 | 7·8 | | 6·5 | 5·5 | 5·9 | | 5·1 | 4·1 | 2·0 | | 1·7 | 1·8 | 1·5 | | 2·2 | 3·2 |
| 2 | 5·5 | 4·4 | | 4·5 | 3·6 | 3·6 | | 3·8 | 2·0 | 1·4 | | 1·4 | 2·8 | 2·6 | | 1·0 |
| 3 | 7·3 | 7·2 | 7·1 | | 6·0 | 6·4 | 6·4 | | 1·3 | 1·0 | 0·8 | | 2·9 | 2·2 | 1·7 | |
| 4 | 5·9 | 4·5 | | | 3·5 | 3·4 | | | 1·2 | 2·0 | | | 5·0 | 4·0 | | |
| 5 | 7·7 | | 6·2 | | 4·8 | | 4·6 | | 2·4 | | 1·5 | | 4·4 | | 2·4 | |
| 6 | 6·5 | | 5·5 | | 4·6 | | 4·6 | | 1·7 | | 1·3 | | 2·0 | | 2·0 | |
| 7 | 6·6 | | 4·6 | | 4·3 | | 3·9 | | 3·0 | | 2·2 | | 2·6 | | 3·0 | |
| 8 | 7·0 | | 6·1 | | 5·1 | | 5·3 | | 1·7 | | 1·3 | | 1·9 | | 1·9 | |
| 9 | 7·5 | 4·3 | | 5·0 | 5·5 | 3·5 | | 4·1 | 2·0 | 1·5 | | 1·4 | 3·3 | 2·5 | | 2·0 |
| 10 | 6·1 | | 5·6 | | 4·5 | | 4·6 | | 1·2 | | 1·2 | | 1·4 | | 1·7 | |
| 11 | 6·9 | | 6·4 | | 4·5 | | 5·5 | | 2·5 | | 1·2 | | 3·9 | | 1·2 | |
| 12 | 6·6 | | 4·9 | | 5·3 | | | 3·8 | 1·8 | | | 1·8 | 1·9 | | | 2·4 |
| 13 | 8·0 | 7·2 | 7·5 | | 5·5 | 6·5 | 5·9 | | 1·5 | 0·8 | 1·3 | | 4·6 | 1·2 | 1·7 | |
| 14 | 7·0 | 6·1 | | 5·6 | 4·1 | 5·4 | | 4·7 | 2·5 | 1·2 | | 1·2 | 5·2 | 0·8 | | 1·6 |
| 15 | 7·9 | | 7·7 | 6·9 | 6·5 | | 6·9 | 6·0 | 1·5 | | 0·8 | 1·5 | 1·8 | | 1·2 | 1·8 |
| 16 | 5·9 | | | 4·9 | 4·6 | | 3·5 | | 1·4 | | 2·2 | | 2·6 | | 5·0 | |
| 17 | 7·2 | | 6·8 | | 5·8 | | 6·0 | | 1·7 | | 0·7 | | 2·9 | | 2·0 | |
| 18 | 8·0 | 6·3 | 6·3 | | 5·4 | 5·5 | 5·1 | | 2·4 | 1·0 | 1·5 | | 4·8 | 1·5 | 1·4 | |
| 19 | 9·0 | | 7·4 | | 7·9 | | 6·7 | | 0·9 | | 0·7 | | 0·8 | | 1·3 | |
| 20 | 6·8 | | | 4·0 | 3·9 | | | 3·3 | 3·1 | | | 1·6 | 6·8 | | | 3·1 |

**Left ventricular dimension**

The mean end-systolic dimension was $5\cdot0\pm1\cdot0$ cm before and $4\cdot7\pm1\cdot0$ cm after operation, which was not significantly different. There was, however, a highly significant drop in end-diastolic dimension from $7\cdot0\pm0\cdot8$ cm to $5\cdot7\pm1\cdot0$ cm 7 days after operation ($P<0\cdot001$). If the 7 patients are considered in whom multiple estimations were performed, it is apparent that this reduction in diastolic dimension occurred very early in the postoperative period, being already significant 2 days after valve replacement ($P<0\cdot01$). A further slight reduction took place between the second and the ninth postoperative day, but this was not statistically significant. Of the patients in whom the reduction in end-diastolic diameter was less than 0·5 cm, 1 had a para-

TABLE 3 *Changes in echo dimension-apex cardiogram loop*

| *Case No.* | *Total area (%) (within loop)* | | | | *Change before 'E' point (%)* | | | | *Change before 'O' point (%)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* | *Preop* | *1–3 days* | *5–6 days* | *8–10 days* |
| 1 | 52 | | 31 | 28 | 7 | | 26 | 39 | 41 | | 45 | 33 |
| 2 | 83 | 53 | | 92 | 11 | 11 | 3 | | 6 | 36 | | 5 |
| 3 | 71 | 76 | 62 | | 3 | 5 | 3 | | 26 | 18 | 35 | |
| 4 | 92 | 84 | | | 1 | 9 | | | 6 | 8 | | |
| 5 | 76 | | 57 | | 7 | | 29 | | 17 | | 14 | |
| 6 | 82 | | 66 | | 6 | | 5 | | 12 | | 29 | |
| 7 | 85 | | 86 | | 5 | | 12 | | 10 | | 5 | |
| 8 | 79 | | 67 | | 7 | | 16 | | 15 | | 24 | |
| 9 | 57 | 58 | | 80 | 1 | 14 | | 13 | 42 | 28 | | 7 |
| 10 | 78 | | 57 | | 13 | | 16 | | 7 | | 27 | |
| 11 | 97 | | 81 | | 2 | | 6 | | 1 | | 12 | |
| 12 | 73 | | | 87 | 1 | | | 1 | 26 | | | 12 |
| 13 | 75 | 66 | 81 | | 2 | 5 | 4 | | 23 | 27 | 15 | |
| 14 | 92 | 48 | | 75 | 4 | 15 | | 6 | 3 | 36 | | 19 |
| 15 | 76 | | 59 | 53 | 1 | | 13 | 9 | 24 | | 29 | 38 |
| 16 | 82 | | 89 | | 3 | | 4 | | 16 | | 6 | |
| 17 | 77 | | 58 | | 6 | | 30 | | 17 | | 30 | |
| 18 | 91 | 73 | 56 | | 6 | 14 | 5 | | 1 | 13 | 38 | |
| 19 | 64 | | 48 | | 2 | | 42 | | 34 | | 10 | |
| 20 | 65 | | | 86 | 25 | | | 4 | 10 | | | 10 |

TABLE 4A *Paired t test between determinations before and after aortic valve replacement in 20 patients*

*(A) Before and 8 ± 4 days after*

| | *No.* | *Before* | *After* | *t* | *P* |
|---|---|---|---|---|---|
| End systolic dimension (cm) | 20 | 5·0 ± 1·0 | 4·7 ± 1·0 | –1·76 | NS |
| End diastolic dimension (cm) | 20 | 7·0 ± 0·8 | 5·7 ± 1·0 | –7·96 | <0·001 |
| Peak shortening rate ($s^{-1}$) | 20 | 1·9 ± 0·6 | 1·4 ± 0·4 | –3·36 | <0·01 |
| Peak lengthening rate ($s^{-1}$) | 20 | 3·1 ± 0·3 | 2·1 ± 1·0 | –2·24 | <0·05 |
| Area inside loop (%) | 20 | 77 ± 12 | 71 ± 15 | –1·57 | NS |
| Area outside upstroke (%) | 20 | 5 ± 5 | 6 ± 13 | 0·17 | NS |
| Area outside downstroke (%) | 20 | 17 ± 12 | 18 ± 11 | 0·43 | NS |

Mean ± standard deviation; NS = Not significant.

TABLE 4B *Paired t test showing sequential changes in 7 patients*

| | *No.* | *Mean difference* | *t* | *P* |
|---|---|---|---|---|
| *Comparison between preoperative and 2 ± 1 days after* | | | | |
| End systolic dimension (cm) | 7 | 0·05 | 0·14 | NS |
| End diastolic dimension (cm) | 7 | –1·16 | –3·36 | <0·01 |
| Peak shortening rate ($s^{-1}$) | 7 | –0·72 | –4·92 | <0·01 |
| Peak lengthening rate ($s^{-1}$) | 7 | –0·15 | –2·44 | <0·05 |
| Area inside loop (%) | 7 | –21·88 | –2·82 | <0·05 |
| Area outside upstroke (%) | 7 | 8·88 | 3·74 | <0·01 |
| Area outside downstroke (%) | 7 | 12·75 | 1·80 | NS |
| *Comparison between 2 ± 1 days after and 7 ± 3 days after* | | | | |
| End systolic dimension (cm) | 7 | –0·35 | –1·75 | NS |
| End diastolic dimension (cm) | 7 | –0·16 | –0·81 | NS |
| Peak shortening rate ($s^{-1}$) | 7 | 0·16 | 1·27 | NS |
| Peak lengthening rate ($s^{-1}$) | 7 | 0·02 | 0·08 | NS |
| Area inside loop (%) | 7 | 18·75 | 2·31 | <0·05 |
| Area outside upstroke (%) | 7 | –10·88 | –3·41 | <0·01 |
| Area outside downstroke (%) | 7 | –10·75 | –1·48 | NS |

prosthetic leak, 2 developed low output states, and 1 had clear evidence of left ventricular disease preoperatively on the basis of a low ejection fraction and a reduced value of peak normalized shortening rate.

## Peak rates of wall movement

The mean values of peak normalized rates of wall movement, both in systole and diastole, were significantly reduced after operation ($P<0{\cdot}01$ and $P<0{\cdot}05$, respectively). This reduction was also apparent in the very early postoperative period, with a slight, though statistically non-significant, increase thereafter. Changes in lengthening rate were noticeably less consistent than those in peak shortening rate (Table 4).

## Isovolumic contraction and early relaxation

There was no significant change in the extent of inward wall movement during the period of isovolumic contraction or in the corresponding area when preoperative and the latest postoperative values were compared. However, early postoperative measurements showed a significant increase in inward wall movement during this period, which regressed over the succeeding 7 to 10 days. In spite of correction of the aortic regurgitation, outward wall movement during early relaxation persisted postoperatively, suggesting the development of additional abnormalities in this period of the cardiac cycle (Fig. 4 and 5). Both these changes resulted in a significant reduction of the area within the loop expressed as a percentage of the whole. These changes were more extensive in 2 patients whose

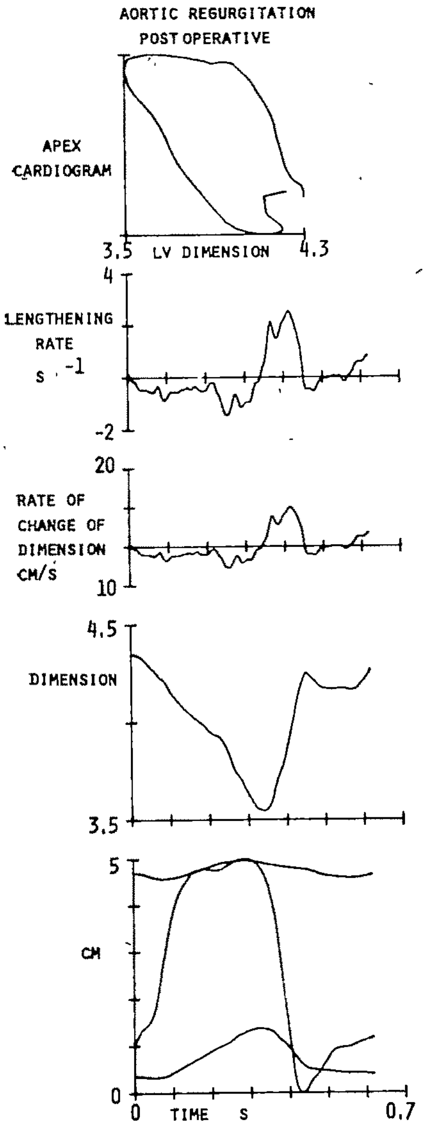

FIG. 4 *Computer output from Case 9, 3 days postoperatively. The layout is the same as for Fig. 2. Abnormal wall movement during the upstroke of the apex cardiogram is now apparent.*

postoperative course was complicated. In 1, a low cardiac output state persisted for 3 to 4 weeks, and throughout there was clear correlation between his clinical state and the configuration of the loop (Fig. 6). The second developed a paraprosthetic leak, and a distorted loop persisted until a second operation. Though all patients had reversed septal movement, this persisted unchanged while the loop improved. There was no correlation, in individual patients, between the duration of cardiopulmonary bypass and any feature of left ventricular function.

## Discussion

Persistence of impaired left ventricular function has been reported in patients 1 month to 2 years after aortic valve replacement, but there is still little information about changes in the early postoperative

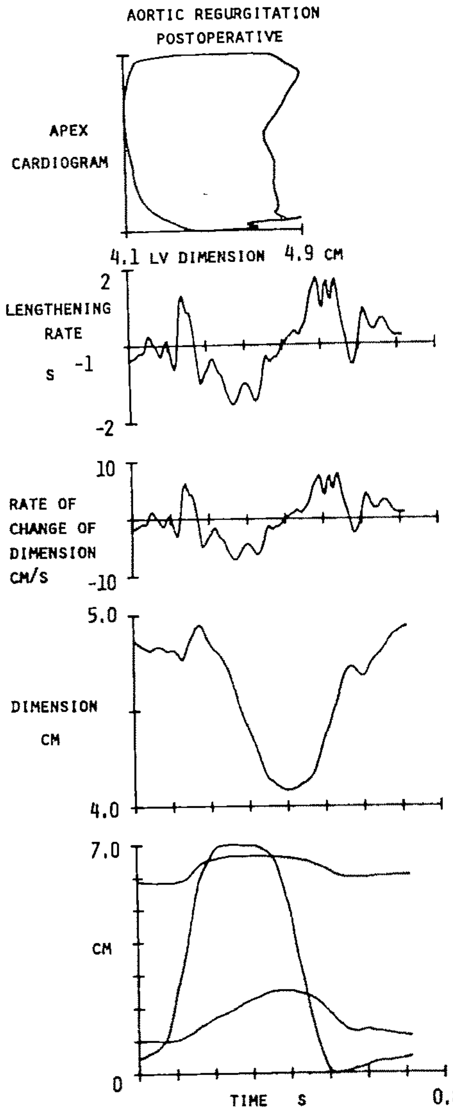

FIG. 5 *Computer output from Case 9, 10 days after operation. There has been partial regression of the abnormalities present at 3 days.*

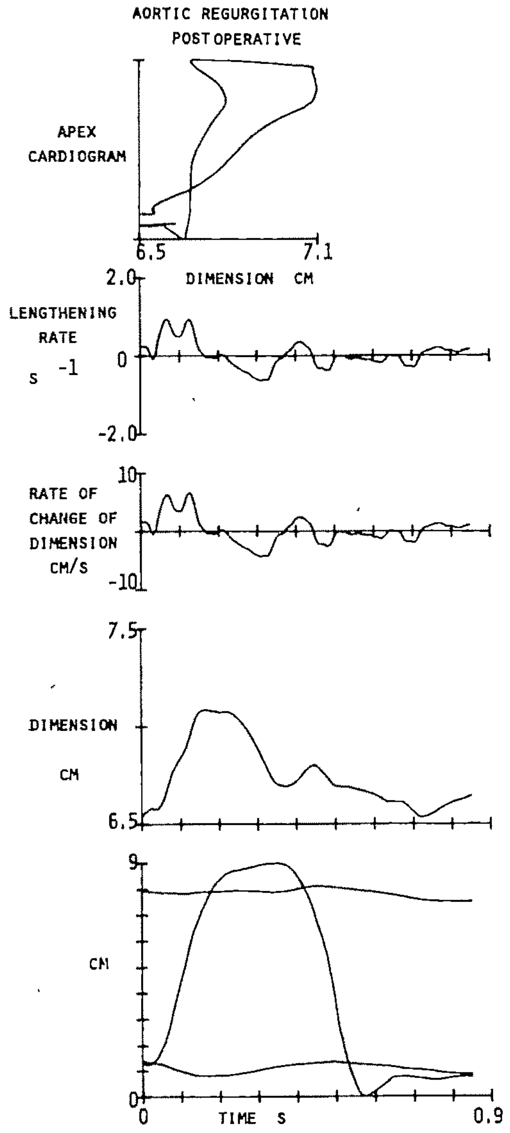

FIG. 6 *Computer output from a patient who developed a low cardiac output state, from a record taken 17 days postoperatively (Case 15). There is reversed movement of the posterior wall, and the echo dimension-apex cardiogram loop is inverted.*

period. This may be related to technical difficulties in making the appropriate measurements. Angiocardiographic techniques do not lend themselves to repeated performance, and in any case, are not feasible immediately after open-heart surgery. Standard haemodynamic measurements have been made by a number of authors (Carey and Plested, 1972; Uhrenholdt *et al.*, 1973), but these may be difficult to interpret: cardiac output or end-diastolic pressure may be affected by transfusion, catecholamine infusion, or pericardial pressure and cannot therefore be taken as directly reflecting the function of the left ventricle. Estimation of systolic time intervals is non-specific and subject to limitations in the postoperative period, particularly when comparison is made with values from normal controls, and when they are dependent on the timing of aortic valve closure, which may be modified by the presence of a prosthetic valve. We have, therefore, based the present study on simultaneous apex and echocardiograms, both of which were relatively easy to perform in the early postoperative period in the patient group studied. The echocardiogram gave information about left ventricular cavity size, peak rates of wall movement, and also the direction of septal movement. With additional information available from the apex cardiogram, it was possible to detect and quantify abnormal wall movement occurring during isovolumic contraction and the period of early relaxation, which have previously been shown to be associated with overall impairment of the function of the left ventricle.

The present study indicated changes in three aspects of left ventricular function apparent in the early postoperative period; reduction in end-diastolic diameter, a drop in peak normalized shortening rate, and abnormalities of wall movement during the early phases of contraction and relaxation. All these changes were apparent within the first 2 days after operation: those in dimension and peak rate of change of dimension persisted virtually unchanged until the end of the study, while those associated with abnormalities of the apex dimension loop tended to regress. The changes in dimension and peak normalized shortening rate are similar to those described by other authors (Gault *et al.*, 1970; Burggraf and Craige, 1975) after longer periods following operation. McDonald (1972), however, had already noted that impairment of shortening of myocardial fibres alone would not explain his observations on the movement of epicardial clips. He noted, in particular, the tendency for base to apex shortening to be more impaired than that along the minor diameter, and suggested the possibility of an underlying change in ventricular architecture. In addition, he observed the presence of reduced shortening or even lengthening of some segments during isovolumic contraction, and during ejection similar abnormalities or premature cessation of shortening occurred. Our findings are compatible with these observations, suggesting that such incoordinate contraction may appear in the early postoperative period, with only partial regression thereafter. If incoordinate left ventricular contraction is indeed a significant aspect of postoperative left ventricular disorder, this finding may have therapeutic implications, since treatment with positive inotropic drugs would not necessarily be expected to have the same beneficial effect as if impaired cardiac function were the result of a uniform depression of contractile state.

The present results also stress difficulties in attempting to quantify left ventricular function in terms of a single 'index' or 'parameter', when a number of separate changes are occurring simultaneously. In the immediate postoperative period, end-diastolic dimension was reduced, suggesting an improvement, while peak shortening rate dropped, indicating a deterioration in left ventricular performance. At the same time, there was evidence of incoordinate left ventricular contraction which was most striking 4 to 5 days after operation and then regressed, while the other variables remained unchanged. It is difficult to see how these changes could have been expressed in terms of a single quantity, however specific or sensitive it may have been. Rather, it is suggested that, in clinical practice, impaired left ventricular function may result from a number of different disturbances. The present study indicates that an initial analysis may usefully be made in terms of changes in ventricular dimension, peak rates of wall movement and contraction pattern, and suggests a non-invasive approach to the problem.

The computer equipment used for this study was provided by the DHSS as part of their experimental computer programme.

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# Heart rate—left ventricular ejection time relations[1]
## *Variations during postural change and cardiovascular challenges*

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*Regression equations for heart rate (HR)—ejection time (LVET) relations provide the appropriate factors for predicting or correcting left ventricular ejection time at any HR. We investigated HR-LVET regressions under different conditions common to both physiological and clinical studies of LVET which had been selected because of predictably different physiological responses. Ten normal subjects were studied during both supine and sitting rest and during isometric handgrip (IHG) in both supine and sitting postures and 10 during head-up tilt. Unexpectedly, as compared with pre-exercise rest on a bicycle ergometer, the slope for the resting state on a chair was slightly flatter, and LVET values were uniformly higher throughout the range of HRs measured.*

*Differences among HR-LVET slopes and intercepts appeared to reflect the established behaviour of stroke volume and ejection rate under the conditions studied. Differences observed among intercepts, especially in supine vs. upright postures, are substantial and require that the appropriate intercept be applied in predicting LVET at a given HR. Differences among slopes, while not statistically significant, may, under practical conditions, lead to unacceptable error if the appropriate slope factor is not used in correcting LVET for HR.*

Left ventricular ejection time (LVET) is often measured to assess left ventricular performance under a variety of conditions (Kesteloot and Denef, 1970; Benchimol and Matsuo, 1971; Parisi, Salzman and Schechter, 1971; Takahashi and Moritz, 1972; Matsuura and Goodyer, 1973). Because LVET is dependent on heart rate (HR) (Braunwald, Sarnoff, and Stainsby, 1958; Jones and Foster, 1964) it is common practice to correct LVET for HR based on linear regression equations. The corrected value, the ejection time index (ETI), is calculated as follows: ETI=LVET—b(HR), where b is the slope of the regression analysis of LVET on HR. By employing the intercept (a) of the regression equation, it is also possible to predict LVET for a given HR using the formula LVET=a+b(HR).

While LVET is HR dependent, the exact relation varies according to factors such as age, sex, and health status (Weissler, Harris, and White, 1963; Harris *et al.*, 1964; Spodick and Kumar, 1968; Kesteloot and Denef, 1970; Willems *et al.*, 1970; Takahashi and Moritz, 1972). Physiological challenges such as supine (Lindquist, Spangler, and Blount, 1973; Maher *et al.*, 1974) and upright (Lance and Spodick, 1976) bicycle exercise also effect differences in the HR-LVET relation. Demonstration of the HR-LVET relations under the different conditions in which LVET must be corrected for HR are of both theoretical and practical importance. They are of theoretical importance as an expression of the underlying physiology of these conditions. They are of practical importance as appropriate factors for correcting data.

To obtain a range of LVET behaviour, we chose

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postural changes, tilt, and isometric exercise because they are simply administered, common noninvasive challenges which evoke predictable cardiac responses (Stevens, 1966; Abelmann and Fareeduddin, 1969; Helfant, DeVillas, and Meister, 1971; Spodick, Meyer, and St. Pierre, 1971; Siegel *et al.* 1972; Fisher *et al.*, 1973). Though LVET has been measured during isometric exercise (Siegel *et al.*, 1972; Quarry and Spodick, 1974) and tilt (Stafford, Harris, and Weissler, 1970; Zambrano and Spodick, 1974) it has been corrected for HR by equations determined under other circumstances, owing to the absence of investigations of the actual HR-LVET regression analysis not only during these conditions but also during rest and stress testing in different postures.

The purpose of this study was to determine HR-LVET regression relations in different postures, including tilt, and during isometric exercise. We studied subjects in the resting state in supine and sitting positions, during isometric handgrip (IHG) in supine and sitting positions and during 70° head-up tilt.

## Methods

All subjects were studied in the morning in the postabsorptive state and after a 30-minute rest period. Ten subjects were studied before and during isometric handgrip exercise in the supine and sitting positions and 10 during 70° head-up tilt. These two groups represented the same population, i.e. both comprised normally active healthy men, aged 22 to 32, none being a trained athlete or a hospital patient. All had a normal history, physical examination, 12-lead electrocardiogram, and chest $x$-ray film.

Recordings included a bipolar electrocardiogram and a right external carotid pulse curve using equipment previously described (Pigott *et al.*, 1971). The electrocardiogram and carotid pulse curve were simultaneously recorded on a Hewlett-Packard optical recorder No. 568-100A at a paper speed of 75 mm/s.

### Recordings

**Supine rest** The supine controls were recorded after 15 to 30 minutes' rest in supine position, just before each of four levels of supine IHG. Thus, 4 supine resting recordings were taken for each of the 10 subjects.

**Sitting rest** The sitting controls were recorded after 15 to 30 minutes rest in a cushioned chair, just before each of 4 levels of sitting IHG. Thus, 4 sitting recordings were taken for each of the 10 subjects.

**Supine IHG** IHG was accomplished by having the subjects squeeze a rolled pressure cuff which had been inflated to 20 mmHg (Quarry and Spodick, 1974). The cuff was connected to a sphygmomanometer, the dial of which provided the feedback for subjects to maintain a constant level of contraction for the duration of each IHG. In order to obtain a wide range of HRs, four levels of IHG were studied. The four levels of IHG consisted of 15, 30, 50, and 100 per cent maximum voluntary contraction (MVC). MVC was established as the maximum pressure developed (as recorded on the sphygmomanometer) out of three trials in which each subject had been instructed to squeeze the rolled cuff as hard as possible. The 15 and 30 per cent MVC were held for 4 minutes with tracings recorded at 30-second intervals; 50 per cent MVC was held for a maximum duration up to 4 minutes, with tracings recorded at 30-second intervals; the maximal level was held for approximately 30 seconds with tracings recorded just before release.

**Sitting IHG** Recordings for sitting IHG were identical to those of supine isometric handgrip, with the single difference being that of posture.

**Tilt** Head-up tilt to an angle of 70° was recorded at 1, 4, and 7 minutes of tilt on a standard NASA tilt table (i.e. padded saddle without foot supports).

### Measurements

HR was determined from the electrocardiogram by dividing 60 000 by the RR interval of the preceding cycle measured in milliseconds. LVET was measured as the time in milliseconds from the rapid upstroke to the incisura of the carotid pulse curve. Five LVETs with corresponding HRs were measured for each subject at each of the recording times indicated above. The mean LVET and HR values of these five beats were determined.

### Statistical analyses

Regression analysis (including slope, intercept, and standard error of estimate) was carried out for each of the conditions under investigation. In order that each subject be used as the experimental unit, mean values within individuals were determined for each of the conditions under investigation, e.g. the mean value of the four supine resting recordings for each of the 10 subjects was determined. Thus, 10 points (one for each subject) were used in the regression analysis for supine rest, and formed the basis for comparisons with other regressions. Similarly, mean values within individuals were determined for sitting rest.

In a previous investigation (Spodick *et al.*, 1971) it was shown that HR and LVET did not vary

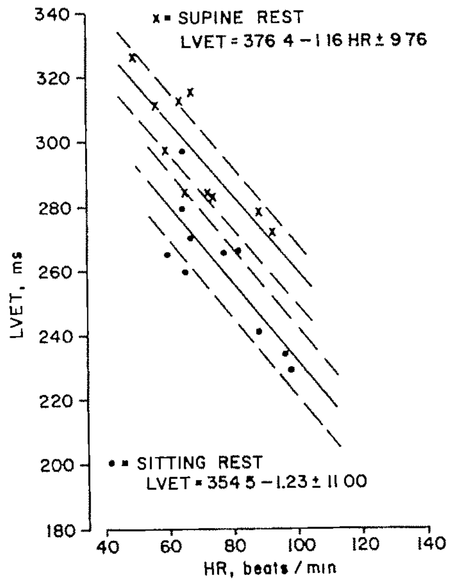

FIG. 1 *Heart rate—left ventricular ejection time relation showing postural effects at rest. Slopes are virtually identical, but intercepts differ considerably. Equations represent regression analysis showing intercept, slope, and standard error of estimate. NB: sitting rest = sitting in cushioned chair (compare Fig. 5).*

among 1, 4, and 7 minutes of tilt. The tilt data were, therefore, handled in the same way as the supine and sitting rest data, with a mean value determined within individuals. Thus, each of the 10 subjects investigated during tilt contributed one point in the regression analysis.

In order to obtain a wide range of HRs, four levels of IHG were studied in both supine and sitting positions. Without sacrificing information yet still having each subject contribute equally in the statistical analysis, the mean values within individuals were determined for (1) 15 per cent, (2) 30 per cent, and (3) 50 and 100 per cent, combined. Regression analyses were performed on each of these levels of IHG. A pooled slope, intercept, and standard error of estimate were then determined for (1) supine IHG and (2) sitting IHG. These two IHG regressions then formed the basis for the comparison with other regressions.

TABLE *HR-LVET regression equations for different conditions*

| | *Intercept* | *Slope* | *Standard error of estimate* |
|---|---|---|---|
| A. Supine rest | 376·4 | −1·16 | ± 9·76 |
| B. Supine isometric handgrip | 381·5 | −1·20 | ± 9·49 |
| C. Sitting rest in cushioned chair | 354 5 | −1·23 | ±11·00 |
| D. Sitting isometric handgrip | 372·1 | −1·32 | ±10·10 |
| E. Tilt | 374 5 | −1 68 | ±12·20 |
| F. Sitting rest on bicycle ergometer | 353 6 | −1·50 | ±11 04 |

## Results

Results are summarized in the Table and illustrated in Fig. 1 to 5.

### Supine rest

The HR-LVET relation for the 10 young adult males during supine rest (before IHG) is shown in Fig. 1. This relation had a slope of −1·16 ms/beat, an intercept at 376·4 ms and a standard error of estimate (SEE) ±9·76.

**Sitting rest** The HR-LVET relation during sitting rest in a cushioned chair (before IHG) for the same 10 subjects as recorded during supine rest is also shown in Fig. 1. This relation had a slope of 1·23 ms/beat, an intercept at 354·5 ms, and SEE ±11·00.

### Supine IHG

The HR-LVET relation during supine IHG for the

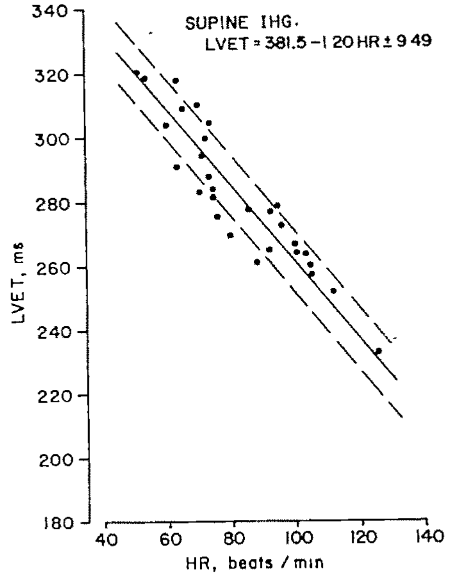

FIG. 2 *Heart rate—left ventricular ejection time relation during isometric handgrip (IHG) exercise in supine position. Measurements cover range of 15, 30, 50, and 100 per cent maximum voluntary contraction.*

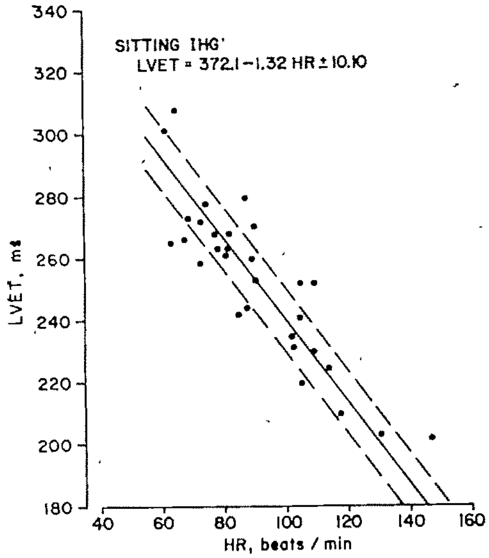

FIG. 3 *Heart rate—left ventricular ejection time relation during isometric handgrip (IHG) exercise in* sitting *position. Measurements cover range of 15, 30, 50, and 100 per cent maximum voluntary contraction.*

same 10 subjects as recorded during supine and sitting rest is shown in Fig. 2. This relation had a slope of −1·20 ms/beat, an intercept at 381·5 ms, and SEE ±9·49.

### Sitting IHG

The HR-LVET relation during IHG in sitting position for the same 10 subjects as recorded during supine and sitting rest and supine handgrip is shown in Fig. 3. This relation had a slope of −1·32 ms/beat, an intercept at 372·1 ms, and SEE ±10·10.

### Tilt

The HR-LVET relation for the other set of 10 young adult men during 70° head-up tilt is shown in Fig. 4. This relation had a slope of −1·68 ms/beat, an intercept at 374·5 ms, and SEE ±12·20.

### Comparison of slopes

The t test for slopes showed no differences among any of the comparisons made. Even the largest difference between tilt (−1·68) and supine rest (−1·16) did not reach significance.

## Discussion

We had previously investigated the HR-LVET relation during supine rest in normal men 21 to 35 years of age (Spodick and Kumar, 1968). The regression equation established at that time was LVET=375·7−1·22 HR, while the supine rest equation determined in the present investigation for a smaller group of men of comparable age and health status, but entirely different subjects, showed LVET=376·4—1·15 HR. In practice, with LVET expressed in milliseconds, investigators have rounded the slope to the nearest tenth to correct LVET for HR (Parisi *et al.*, 1971; Maher *et al.*, 1974; Quarry and Spodick, 1974). Both these slopes thus round to 1·2 ms/beat yielding, for practical purposes, virtually identical equations.

### Supine rest vs. sitting rest

In comparing the resting HR-LVET relation in supine and sitting positions (Fig. 1; Table—A, C) it is apparent that the slopes are similar, with similar scatter around the regression line, as evidenced by the comparable standard errors of estimate. The single important difference is that the curve during sitting rest is uniformly lower and consequently has an intercept which lies lower on the ordinate than that of supine rest (a difference in intercepts of 21·9 ms). Since LVET varies directly with stroke volume (SV) this difference appears to reflect the known reduced SV with upright, as compared with supine posture (Bevegård, Holmgren, and Jonsson, 1963; Grimby, Nilsson, and Sanne, 1966; Astrand

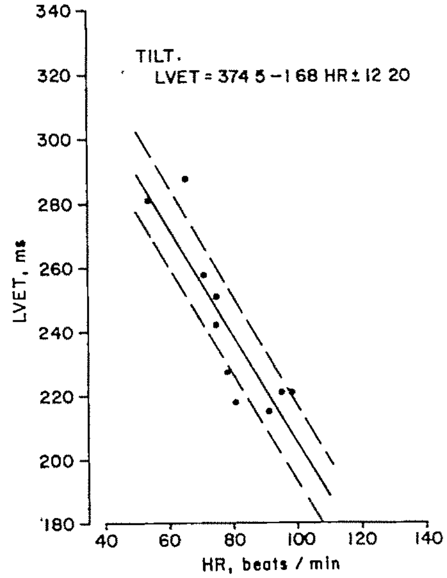

FIG. 4 *Heart rate—left ventricular ejection time relation during 70° head-up tilt.*

and Rodahl, 1970). The fact that the two curves parallel one another suggests that if other variables affecting LVET are present, they must affect the LVET in a direction and magnitude which is similar for both supine and sitting rest.

### Control vs. IHG

A statistical comparison of supine resting values with those of supine IHG shows no difference between slopes, while differences between intercepts and standard errors of estimate are small (Table—A, B). Likewise, a comparison of sitting rest with sitting IHG shows essentially the same similarities between curves (Table—C, D). The effects of IHG on SV have been reported and vary from small increases (Fisher *et al.,* 1973) to no change or even decreases at higher levels of contraction (Lind, 1970), while ejection rate has been shown to decrease in the presence of a high afterload (Braunwald *et al.,* 1958). Whether the changes in these variables during IHG were minimal or had opposing effects (e.g. reduced SV would shorten LVET, while reduced ejection rate would lengthen LVET) is not clear from our data. However, the important finding, to which this study is addressed, is that it appears that factors associated with IHG in either supine or sitting position do not alter the HR-LVET relation from that of the control state.

### Supine IHG vs. sitting IHG

A comparison of postural effects on IHG yields similar findings to those of the postural differences during rest. Again, similar HR-LVET slopes occur during supine and sitting IHG (Table—B, D). As with supine vs. sitting rest, however, the curve during sitting IHG remains uniformly lower and thus has a lower intercept than that during supine IHG, a difference which again appears to reflect the smaller SV with upright posture noted previously. Since IHG was performed at identical stress levels in both sitting and supine positions, the data in both postures should represent comparable physiological challenges. Thus, once resting postural differences are taken into account, the increases over resting levels in variables such as cardiac output and adrenergic activity should be comparable during IHG for both supine and sitting postures. The similar HR-LVET slopes for both conditions support such comparability and suggest that determinants of LVET (such as SV and mean rate of ejection) do not act in a disproportionate fashion during IHG in supine as compared with sitting position.

### Tilt vs. rest and IHG

The slope during tilt tended to be greater than the slopes of the other four conditions studied in this investigation, but the differences between tilt vs. supine and sitting rest and supine and sitting IHG were not significant. The 95 per cent confidence interval of the slope for tilt is $-1 \cdot 168 \pm 0 \cdot 679$. Thus, the difference between tilt and the other slopes may be less or substantially greater with additional observations. An important consideration, however, should be the practical implications of this difference between slopes, e.g. if a slope factor of 1·2 (supine rest) rather than the observed tilt slope of 1·68 were multiplied by HRs recorded during tilt (range of 55 to 101 beats per minute), the resultant corrected ejection time would be substantially underestimated. Since ETI is determined in order to evaluate other factors (principally SV) affecting LVET, inappropriate conclusions regarding cardiac function may also be drawn. Thus, the importance of using appropriate correction factors is clear.

The regression line for LVET on HR during tilt was below that during rest and IHG within the range of HRs studied. This finding is consistent with the expected large reduction in SV in tilted normal subjects (Zambrano and Spodick, 1974). The sharper slope for tilt reflects a progressively larger reduction in LVET with higher HRs during tilt as compared with rest and IHG (Table). This could represent a disproportionate reduction in SV with increasing HRs during head-up tilt. Increased ejection rate via improved contractility or Starling effect would also explain decreased LVET (Braunwald *et al.,* 1958). However, tilt does not appear to change contractility (Paley *et al.,* 1971) and reduces preload (Abelmann and Fareeduddin, 1969). Improved ejection rate, therefore, does not seem to be a factor effecting the progressively greater shortening of LVET with increasing HR during tilt as compared with rest and IHG.

### Sitting controls

In a previous investigation (Lance and Spodick, 1976) we studied the HR-LVET relation during rest, before bicycle exercise, with subjects seated on the bicycle ergometer and feet resting on the pedals. The subjects were entirely comparable to those in this study.

The slopes do not differ significantly; Fig. 5 shows the slope to be steeper and LVETs uniformly lower for subjects seated on the bicycle ergometer than that for subjects seated in a chair. The 95 per cent confidence interval for the slope for bicycle ergometer sitting is $-1 \cdot 50 \pm 0 \cdot 629$—again suggesting that the difference between slopes for sitting rest on a chair vs. on a bicycle ergometer may be less or substantially greater. The intercepts for the two

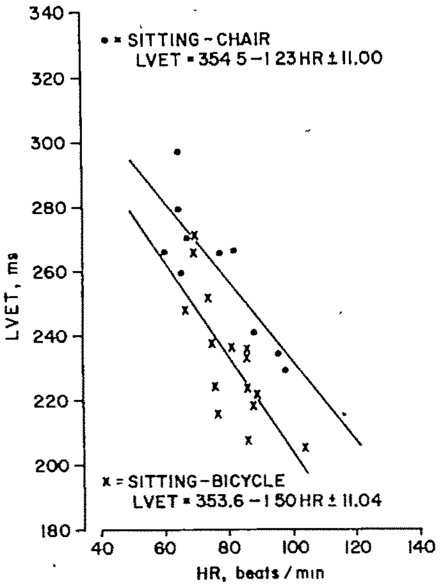

FIG. 5 *Comparison of heart rate—left ventricular ejection time relations during upright rest: sitting in chair versus sitting on bicycle ergometer.*

conditions are similar, but this is because of the steeper slope with bicycle sitting.

Data have been reported for 'sitting rest', but these have included not only chair but bicycle ergometer (Bevegård *et al.*, 1963) without accounting for or acknowledging potential differences between the two. As was pointed out in the discussion of tilt, if the slope factor is used to correct LVET for HR, even slope differences of the magnitude here observed can, in practice, lead to substantially different results—and conclusions. It, therefore, seemed important to point out these potential differences and the possibilities of errors if the two 'resting states' are used interchangeably.

## Conclusions

Comparison of the heart rate-ejection time relation during supine and sitting rest on both a chair and a bicycle ergometer, during isometric handgrip in both supine and sitting postures, and during head-up tilt, reveal differences among the respective regression equations, which can be explained by the well-established differences in stroke volume and ejection rate among these states. These differences appear to account for the fact that under conditions in which stroke volume variations should be the major determinant, slopes will be similar, but intercepts will vary. Thus, our regression lines for supine versus sitting rest in a chair, for example, have similar slopes, but the line for sitting rest remains uniformly below that for supine rest. Similar trends are also indicated for supine versus sitting isometric exercise; the curves parallel each other, but the curve for sitting IHG remains below that of supine IHG, apparently entirely because postural reduction of SV in the sitting position (Astrand and Rodahl, 1970; Bevegård *et al.*, 1963; Grimby *et al.*, 1966). In contrast, during pre-exercise upright rest on the bicycle ergometer, there is a tendency toward a sharper decrease in LVET at increased heart rates and, hence, a somewhat steeper regression slope than for other resting conditions. It appears that when increases in HR accompany greater increases in stimuli which reduce SV or increase ejection rate, the HR-LVET slope becomes sharper.

Because of potential differences, it is suggested that clinicians and researchers use correction factors appropriate to the conditions being studied. Furthermore, since substantial differences among intercepts are presented, caution should be applied if the intercept factor is used to predict LVET for HR.

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# Plasma zinc in acute myocardial infarction
## *Diagnostic and prognostic implications*

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*Zinc is a metal component of many important enzymes, and its availability controls the rate of synthesis of nucleic acids and protein. Serum zinc levels have been shown to fall after acute tissue injury, including myocardial infarction.*

*The purpose of this clinical study was to examine the value of serial plasma zinc measurements in a coronary care unit. Studies were made on 188 patients: 88 with unequivocal myocardial infarction, 52 controls, and 48 in a borderline group.*

*Patients with myocardial infarction showed a fall in plasma zinc within the first three days, whereas patients in the other two groups did not. The difference in the mean minimum zinc levels between the groups with and without infarction was highly significant.*

*In patients with myocardial infarction there was good correlation between the minimum plasma zinc level and the peak value of plasma enzymes, and also with some clinical estimators of prognosis. A fall in plasma zinc is a reliable diagnostic test for acute myocardial infarction, and the extent of the fall has prognostic implications.*

Zinc is the metal component of many important enzymes, including carbonic anhydrase, alkaline phosphatase, various proteases, and many dehydrogenases (Wacker, Ulmer, and Vallee, 1956; Li, 1966; Orten, 1966). The availability of zinc governs the tissue concentrations and activity of zinc metallo-enzymes, and also the rate of synthesis of nucleic acids and protein.

Serum zinc levels have been shown to fall after acute tissue injury (Halsted and Smith, 1970), including myocardial infarction (Wacker *et al.*, 1956; Halsted and Smith, 1970; Lindeman *et al.*, 1973; Handjani *et al.*, 1974). In myocardial infarction the levels fall within one or two days of the onset, and then rise to reach normal levels in 10 to 14 days. The clinical studies reported so far (Wacker *et al.*, 1956; Handjani *et al.*, 1974) have investigated relatively small numbers of patients, and there has been little attempt to correlate the zinc levels with other biochemical measurements, or with prognosis. Thus, it is not yet established whether measurement of plasma zinc has any practical value in myocardial infarction.

The purpose of this study was to examine within the context of a coronary care unit the value of serial plasma zinc measurements. The first objective was to evaluate the usefulness of this test in distinguishing patients with acute myocardial infarction from those with chest pain not due to infarction. The second was to study the relation between plasma zinc and other biochemical and clinical prognostic indices usually measured in myocardial infarction.

## Subjects and methods

### Methods

The 206 patients admitted to the Coronary Care Unit of the Princess Margaret Hospital between August 1974 and January 1975 were the subject of this study.

Blood was collected for investigations on the first, second, third, and tenth day without regard to the fasting state. It was collected in plastic syringes, avoiding haemolysis and contamination by metals.

Creatine kinase (CK) was measured by a kinetic method using the Vitatron[1] apparatus. Serum aspartate aminotransferase (AST), lactic dehydrogenase (LDH), and hydroxybutyric dehydrogenase

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[1] Made by Vitatron, Holland.

(HBD) were measured by the colorimetric method, using kits. Plasma zinc was measured by atomic absorption spectrophotometry, after precipitating plasma protein with trichloracetic acid (Hackley *et al.*, 1968).

Statistical analysis of the data was performed on the University of Canterbury Burroughs Computer, using standard programmes.

### Patient groups

Patients were included in this study if at least two measurements of plasma enzymes and zinc were obtained between the first and third days after admission. Adequate data were obtained in 188 patients out of 206 consecutive admissions. These 188 patients were divided into three groups as shown in Table 1.

TABLE 1 *Patient groups*

| | | |
|---|---|---|
| 1 | Acute myocardial infarction | 88 |
| | 1A—Without cardiac arrest or death | 70 |
| | 1B—With cardiac arrest and/or death | 18 |
| 2 | Control group | 52 |
| 3 | Intermediate group | 48 |

Group 1 consisted of 88 patients with unequivocal myocardial infarction. This group was further subdivided into group 1A comprising 70 patients without major arrhythmic complications (ventricular fibrillation or asystole) or mortality, and group 1B comprising 18 patients who suffered reversible cardiac arrest or who died. The diagnosis of myocardial infarction was based on a characteristic history, sequential electrocardiographic abnormalities, and a diagnostic rise in plasma enzymes.

Group 2, consisting of 52 patients, was the control group. All these patients had normal serial enzymes and electrocardiograms recorded daily for 3 days. No evidence of cardiac muscle injury emerged during the week-long period of hospital observation. Hence their chest pain was considered not to be the result of cardiac infarction. However, in the absence of coronary angiographic studies, cardiac ischaemia without infarction as a cause of the pain cannot be conclusively excluded.

Group 3 was an intermediate group of 48 patients who had an equivocal rise in plasma enzymes, and/or electrocardiograms which showed ischaemic changes. It is probable that a number of these patients suffered prolonged ischaemic pain without actual infarction.

## Results

In those patients who had sustained cardiac infarction (group 1) the plasma zinc level fell within the first three days after infarction (Table 2) and then rose to normal or near-normal levels by the tenth day. Patients in groups 2 and 3 did not show this fall.

TABLE 2 *Mean daily plasma zinc levels (μg/100 ml)*

| *Group* | *Day 1* | | *Day 2* | | *Day 3* | | *Day 10* | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| 1 | 92·53 | 17·66 | 79·32 | 13·87 | 76·83 | 17·09 | 96·32 | 9·45 |
| 2 | 96·95 | 16·67 | 97·43 | 17·14 | 95·71 | 17·31 | 100·11 | 9·60 |
| 3 | 88·25 | 11·22 | 90·28 | 12·15 | 90·03 | 12·07 | 96·92 | 11·00 |

Normal range=90–118 μg/100 ml.
*Conversion from Traditional Units to SI units:*
1 μg/100 ml ≈ 0·153 μmol/l.

### Diagnostic implications

The usefulness of plasma zinc in diagnosis of myocardial infarction was ascertained by comparing the mean minimum plasma zinc levels in the three groups (Table 3). There was a highly significant difference between the mean minimum plasma zinc levels of group 1 and group 2, and also between group 1 and group 3. There was no significant difference between the mean minimum plasma zinc levels of groups 2 and 3. When group 1 was further subdivided into groups 1A and 1B the difference between these two subgroups was also highly significant.

TABLE 3 *Minimum plasma zinc levels*

| *Group* | *Number* | *Minimum plasma zinc* (μg/100 ml)<br>*Mean* | *Standard deviation* | *Standard error of mean* |
|---|---|---|---|---|
| 1 | 88 | 68·63 | 14·63 | 1·56 |
| 1A | 70 | 72·07† | 12·25 | 1·46 |
| 1B | 18 | 55·22† | 15·73 | 3·71 |
| 2 | 52 | 84·52* | 12·26 | 1·70 |
| 3 | 48 | 84·60* | 11·58 | 1·67 |

*Significant difference from Group 1 ($P < 0·001$)
†Significant difference between Groups 1A and 1B ($P < 0·001$)
*Conversion from Traditional Units to SI units:*
1 μg/100 ml ≈ 0·153 μmol/l.

### Correlation with plasma enzymes

The zinc results for patients with myocardial infarction (group 1) were compared with the results of other laboratory tests used in this context, namely the enzymes CK, AST, LDH, and HBD.

Statistical analyses were made with both the minimum plasma zinc level and the change in plasma zinc (the difference between the highest and lowest measurement in each patient). The peak level of each of the enzymes was used, and when this was above the usually-measured range, the upper limit of the range was used for the purposes of analysis.

Each enzyme correlated significantly with both the minimum plasma zinc level and the change in plasma zinc, and most of these correlated at a highly significant level (Table 4).

TABLE 4 *Correlation between plasma zinc and plasma enzymes*

| | *Group* 1 (*n*=88) | | | |
|---|---|---|---|---|
| | *Minimum zinc* | | *Change in zinc* | |
| | *r* | *P* | *r* | *P* |
| CK | –0·36 | 0·001 | 0·42 | 0·001 |
| AST | –0·22 | 0·05 | 0·34 | 0·001 |
| LDH | –0·34 | 0·001 | 0·49 | 0·001 |
| HBD | –0·22 | 0·05 | 0·38 | 0·001 |

## Prognostic implications

In order to determine the usefulness of plasma zinc levels in assessing prognosis after myocardial infarction, prognosis in group 1 was judged by the severity of arrhythmias, the number of days spent in hospital after myocardial infarction, and by a coronary prognostic index (Norris *et al.,* 1970).

Arrhythmias were graded on an arbitrary scale from 1 to 5. Grade 1 represented trivial or no arrhythmia (32 cases), grade 2 a significant arrhythmia requiring treatment (30 cases), grade 3 a potentially life-threatening arrhythmia (8 cases), grade 4 cardiac arrest successfully treated (8 cases), and grade 5 death (10 cases). There is a downward trend in the mean minimum zinc level with increasing severity of arrhythmia (Fig.), and on overall analysis this correlation is highly significant.

For those patients with myocardial infarction who survived, the correlation between the minimum plasma zinc level and the duration in hospital was also highly significant (P < 0·001).

There was a highly significant correlation between the minimum plasma zinc level and an accepted coronary prognostic index (Norris *et al.,* 1970).

## Discussion

Our results confirm the findings of previous workers (Wacker *et al.,* 1956; Halsted and Smith, 1970; Lindeman *et al.,* 1973; Handjani *et al.,* 1974) that plasma zinc falls in myocardial infarction. Myocardial necrosis can, therefore, be distinguished from ischaemia and non-cardiac chest pain.

Although plasma zinc changes lack specificity in general, in the context of a coronary care unit these may be taken as a reliable test of infarction.

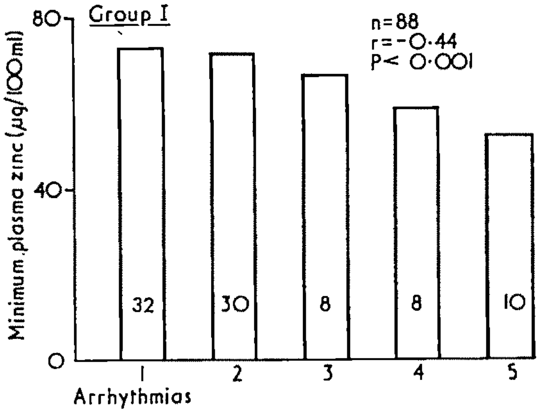

FIG. *Minimum plasma zinc and arrhythmias. (1 µg/100 ml ≈ 0·153 µmol/l.)*

The specificity of plasma zinc estimation as a diagnostic test in myocardial infarction may be estimated by using Bayes' theorem (Katz, 1974). In patients admitted to our coronary care unit the probability of a positive zinc test (minimum plasma zinc below 75 µg/100 ml with a fall in the first three days) representing myocardial infarction was 80 per cent.

The minimum plasma zinc showed a significant correlation with both enzymes and clinical indices of prognosis. The magnitude of the change in plasma zinc showed a significant correlation with the plasma enzymes only. We conclude that the minimum plasma zinc level is the most clinically useful measure of plasma zinc changes in acute myocardial infarction.

The correlation between change in plasma zinc and enzymes was good for LDH, fair for CK, and poor for AST. Since LDH is a zinc-containing metalloenzyme its closer correlation is understandable. The CK is often altered for non-cardiac reasons, e.g. intramuscular injection (Scott *et al.,* 1974) and hence was less closely related. The poor correlation with AST has no obvious explanation.

The time course of changes in plasma zinc is particularly fortunate for the diagnosis of myocardial infarction. Since the level falls in the first few days and does not return to normal levels for 1½ to 2 weeks, it enables both acute and recent infarcts to be detected.

The measurement of plasma zinc is technically simple, and cheaper than many routine enzyme tests, provided a trace metal laboratory is available. Plasma zinc has the added advantage of not being altered by minor tissue damage or by intramuscular injections.

The precise reason why plasma zinc falls in acute myocardial infarction is still unknown. Plasma zinc has been shown to fall after administration of steroids (Flynn *et al.*, 1971). It is possible that the fall after myocardial infarction may be steroid-related, though the peak in plasma cortisol occurs within the first 12 hours (Bailey, Abernethy, and Beaven, 1967), while the fall in plasma zinc takes somewhat longer.

Studies of heart muscle have shown no real change in the zinc concentration of infarcted muscle compared with normal myocardium (Chipperfield and Chipperfield, 1973). However, increases have been shown in the subcellular fractions where synthesis and storage of enzymes occurs, and it is thought that this might be the result of an increase in enzyme synthesis, in an effort to promote repair (Lindeman *et al.*, 1973). This redistribution of zinc cannot account for the zinc that disappears from the plasma which is thought to be taken up by the liver, and perhaps by other visceral organs also (Lindeman *et al.*, 1973). During stress there is release of a humoral factor produced by polymorphs (leucocyte endogenous mediator, or LEM), which depresses plasma zinc levels, and increases zinc uptake by the liver (Pekarek, Wannemacher, and Beisel, 1972). An alpha$_2$-macroglobulin containing a large amount of zinc has been isolated, and proposed as a transport protein (McBean *et al.*, 1974). The level of this carrier protein is raised in myocardial infarction and other states associated with a fall in plasma zinc.

The data presented in this study indicate that a fall in plasma zinc is a useful empirical diagnostic test for myocardial infarction. The extent of the fall correlates well with the rise of plasma enzymes, and also with some clinical estimates of prognosis.

The postulated importance of zinc in wound healing even if only in zinc-deficient states (Henkin, 1974) suggests that zinc may play a more fundamental role in recovery after myocardial infarction. Thus the intriguing question arises as to whether administration of zinc to patients with myocardial infarction might improve prognosis.

We are grateful to Mrs. D. Hinton for the zinc measurements and Mr. D. Benson-Cooper and Mr. P. Bones for the statistical analyses.

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# Chronic His bundle block
## *Clinical, electrocardiographic, electrophysiological, and follow-up studies on 16 patients*

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*This report describes 16 patients with block within the His bundle seen over a period of 55 months. Ten were women and 6 men, with an average age of 76 years, range, 42 to 98 years. All patients had His bundle recordings showing split His bundle potentials ( H and H′) (13 patients) or narrow QRS with block distal to the His bundle potential (3 patients). Of the 16 patients, 10 had complete heart block, 4 second degree AV block (2 patients with Mobitz type II, and 2 with 2:1), and 2 first degree AV block. Ten patients had a narrow QRS in the conducted beats or escape rhythms. Intravenous atropine (1 to 2 mg) had a variable effect on AV conduction and the rate of the escape rhythm. Twelve patients have had a permanent pacemaker implanted. During the follow-up period, 10 patients died 1 to 31 months from the time of initial examination. The remaining 6 patients (5 with pacemaker) are alive 3 to 58 months later.*

Since the initial description of block within the His bundle by Narula and Samet (1970), several electrophysiological and pathological reports have appeared (Rosen *et al.*, 1970, 1971, 1972, 1973; Narula *et al.*, 1971; Schuilenburg and Durrer, 1972; Gupta, Lichstein, and Chadda, 1972, 1973; Bharati *et al.*, 1974; Narula and Samet, 1974). However, there are no reports on the natural history or long-term follow-up of patients with chronic His bundle block. We present here the clinical, electrocardiographic, electrophysiological, and follow-up data on 16 patients with chronic His bundle block seen over a period of 55 months.

## Subjects and methods

Sixteen patients with documented His bundle block seen between June 1971 and January 1976 form the basis of this report. Five of these patients have been reported previously (Gupta *et al.*, 1972, 1973). All patients were studied and followed at City Hospital Center at Elmhurst, a 1000-bed Municipal hospital. The clinical features are summarized in Table 1. Hypertension was diagnosed if two or more blood pressure determinations had shown a systolic pressure greater than 140 mmHg and a diastolic pressure greater than 90 mmHg, or if the patient had been treated for hypertension before being admitted to hospital. Arteriosclerotic heart disease was diagnosed when there was electrocardiographic evidence of myocardial infarction or a typical history of angina pectoris. Cardiomegaly was considered to be present when the cardiothoracic ratio was greater than 0·5. Criteria for congestive heart failure included presence of dyspnoea on exertion, peripheral oedema, raised venous pressure, and râles.

The following electrocardiographic criteria were used. First degree AV block was present when the PR interval was greater than 0·20 s. Mobitz type II block was diagnosed when there was sudden block of the P wave without change in the preceding PR intervals. 2:1 and 3:1 AV blocks were not defined as to type. Complete heart block was diagnosed when there was complete AV dissociation and the ventricular rate was slower than the atrial rate. Right bundle-branch block and left bundle-branch block were defined according to New York Heart Association criteria (1969).

His bundle electrograms were recorded using the technique of Scherlag *et al.* (1969). Two or more leads of the surface electrocardiogram were recorded

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TABLE 1 *Clinical, electrocardiographic, and follow-up data*

| *Case No.* | *Age, sex* | *Clinical diagnosis* | *Dizziness and syncope* | *Electrocardiogram Degree and type of AV block* | *QRS morphology* | | *Reason for pacemaker* | *Follow-up (mth)* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Conducted beats* | *Escape rhythm* | | | |
| 1 | 84 M | | Syncope | First degree | Narrow, LAH | | Syncope | 3 | Died (outside hospital) |
| 2 | 78 M | AVD, cardiomegaly | Syncope | First degree | LBBB | | Syncope | 3 | Alive |
| 3 | 72 F | ASHD, CHF, hypertension, cardiomegaly | | (Oct '71) 2:1 and Mobitz type II | Narrow, LAH | | CHF | 53 | Alive |
| | | | | (Jul '73) 2:1 | Narrow, LAH | | | | |
| | | | | (Jul '75) CHB | | Narrow, LAH | | | |
| 4 | 57 F | Hypertension, CHF, cardiomegaly | Dizziness | (Nov '71) 2:1 | Narrow | | CHF | 31 | Died, cerebrovascular accident |
| | | | | (Nov '72) CHB | | Narrow | | | |
| 5 | 42 F | Hypertension, cardiomegaly | | Mobitz type II | Narrow, LAH | | Refused | 15 | Alive |
| 6 | 89 M | ASHD, AVD, cardiomegaly | Syncope | 2:1 | LBBB | | Syncope, CHF | 2 | Died, sudden pacemaker malfunction suspected |
| 7 | 80 F | CHF, hypertension | | (Jun '71) CHB | | Narrow | CHF | 58 | Alive |
| | | | | (Jun '75) CHB | | RBBB, LAH | | | |
| 8 | 87 F | CHF, hypertension | Syncope | CHB | | Narrow | Refused | 3 | Died (outside hospital) |
| 9 | 85 M | CHF, cardiomegaly | Syncope | CHB | | RBBB | Syncope, CHF | 43 | Alive |
| 10 | 81 M | ASHD, CHF, hypertension, cardiomegaly | | CHB and 2:1 | RBBB | RBBB | CHF | 14 | Died, cancer of lung |
| 11 | 77 F | CHF, cardiomegaly | Syncope | CHB and 2:1 | Narrow | Narrow | Syncope | 1 | Died, dehydration and emaciation |
| 12 | 73 M | AVD, CHF, cardiomegaly | Syncope | CHB and 2:1 | Narrow | Narrow | Refused | 1 | Died, sudden |
| 13 | 54 F | Hypertension, cardiomegaly | | CHB and 2:1 | Narrow, RBBB | RBBB | Prophylactic | 19 | Died, chronic renal failure |
| 14 | 88 F | ASHD, cardiomegaly | Syncope | CHB and 2:1 | RBBB, LAH | RBBB, LAH | Refused | 15 | Died (outside hospital) |
| 15 | 98 F | Cardiomegaly | Syncope | CHB | Narrow | Narrow, RBBB | Syncope | 2 | Died, dehydration and emaciation |
| 16 | 74 F | Hypertension, cardiomegaly | | CHB | | Narrow | Prophylactic | 3 | Alive |

*Abbreviations:* AVD, aortic valve disease; ASHD, arteriosclerotic heart disease; CHF, congestive heart failure; CHB, complete heart block; LAH, left anterior hemiblock; RBBB, right bundle-branch block; LBBB, left bundle-branch block.

simultaneously with the intracardiac electrogram on a multichannel photographic recorder at paper speeds of 75 to 150 mm/s (Electronics for Medicine DR-12, White Plains, New York). His bundle potentials were validated by noting the position of the recording electrode fluoroscopically. In addition, the pacemaker catheter was gradually advanced and withdrawn alternately, and the presence or absence of His bundle potential was checked as recommended by Schuilenburg and Durrer (1975). Right atrial pacing and His bundle pacing were also used in several patients for validation of the His bundle potential. AH and HV intervals and HH′ intervals were measured as described previously (Gupta *et al.*, 1973). The normal values of AH interval in our laboratory range from 70 to 140 ms and of HV interval from 35 to 55 ms. In 8 patients, 1 to 2 mg intravenous atropine sulphate was given.

Patients were subsequently examined at regular intervals in the cardiac clinic of City Hospital Center. Intrinsic cardiac rhythm in patients with a permanent cardiac pacemaker was evaluated by an external chest wall stimulation method (Barold *et al.*, 1970). Information concerning death outside hospital was obtained from members of the family.

## Results

There were 10 women and 6 men whose ages ranged from 42 to 98 years, with an average age of 76 years. Arteriosclerotic heart disease was present in 7 patients and cardiomegaly in 12. Three patients had

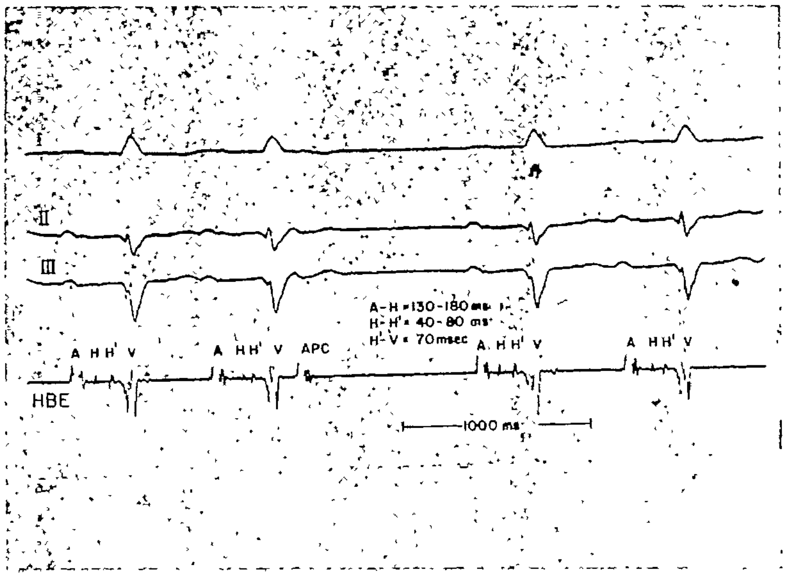

FIG. 1 *His bundle electrogram with simultaneous leads I, II, and III from Case 6 during 1:1 AV conduction. The third atrial beat is premature and is blocked at the AV node. The AH and HH' intervals vary with the cycle length.*

evidence of aortic valve disease. Seven were in congestive heart failure at the time of initial examination. Dizziness or syncope had occurred in 10.

## Electrocardiographic analysis

First degree AV block was seen in 2 patients: the QRS complexes were narrow in one and wide in the other. Second degree AV block was seen in 4 patients at the time of initial evaluation (2 patients with Mobitz type II block and 2 patients with 2:1 AV block): the QRS complexes were narrow in 3 and wide in 1 of these 4 patients (Fig. 1).

Complete heart block was present in 10 patients. In 5, the conduction abnormality was fixed, but in the remaining 5, 2:1 AV block alternated with complete heart block. One patient (Case 9) with fixed complete heart block had shown 2:1 AV block at another hospital a year before the His bundle study. The QRS complexes of the escape beats were narrow in 6 of the 10 patients with complete heart block, and wide in the remaining 4. One patient (Case 7) who initially had narrow escape beats developed wide escape complexes 4 years after the initial study. The rate of the escape rhythm in the 10 patients with complete heart block ranged from 37 to 57, with an average of 41 beats/minute.

## Electrophysiological data (Table 2 and Fig. 2)

The AH interval was measured in all patients and ranged from 70 to 250 ms. In 4 patients, the AH interval was greater than 140 ms. H' could only be recorded in 13 patients. In 2 patients with first degree AV block, the H'V interval was 70 and 50 ms; the HH' interval in these 2 patients was 38 and 40 ms, respectively. Of the 4 patients with second degree AV block, H' could be recorded in 3 and block in each of these occurred distal to H; the H'V interval in these patients ranged from 35 to 70 ms. In 1 patient (Case 3) with second degree AV block, no H' could be recorded and the dropped beats occurred distal to H, thus localizing the block to the distal part of the His bundle; the initial HV interval of 50 ms in this patient had increased to 70 ms at repeat study 20 months later; this patient subsequently developed complete heart block. Another patient (Case 4) with second degree block progressed to complete heart block during the follow-up period. Of the 10 patients with complete heart block, a split His bundle potential was seen in 8, and in these the H'V interval ranged from 40 to 70 ms. In one patient (Case 15) with narrow QRS complexes, block occurred distal to H and the HV interval could not be measured. In another patient (Case 13) without split His potential, HV interval in conducted beats was 90 ms.

TABLE 2 *Electrophysiological data*

| *Case No.* | *Atrial rate (beats/min)* | *Ventricular rate (beats/min)* | *AH (ms)* | *HH′ (ms)* | *H′V (ms)* | *Site of block* | *Effect of atropine* |
|---|---|---|---|---|---|---|---|
| 1 | 70 | 70 | 85 | 38 | 70 | Between H and H′ | |
| 2 | 68 | 68 | 230 | 40 | 50 | At AV node and between H and H′ | |
| 3 | 82 (Oct '71) | 41 | 120 | | 50 (H-V) | 2:1 distal to H | 2:1 block unchanged |
| | 90 (Jul '73) | 45 | 115 | | 70 (H-V) | 2:1 distal to H | 2:1 to 3:1 |
| 4 | 94 (Nov '71) | 47 | 95 | 30 | 35 | 2·1 between H and H′ | 2:1 to 3:2 |
| | 70 (Nov '72) | 36 | 90 | | 35 | CHB between H and H′ | |
| 5 | 85 | 85 | 90 | 25 | 35 | 2:1 and type II between H and H′ | 2:1 to 1:1 |
| 6 | 80 | 80 | 130–180 | 40–80 | 70 | At AV node and between H and H′ | |
| 7 | 68 | 36 | 95 | | 40 | CHB between H and H′ | |
| 8 | 90 | 40 | 70 | | 40 | CHB between H and H′ | No response |
| 9 | 83 | 34 | 90 | | 45 | CHB between H and H′ | VR 34 to 39/min |
| 10 | 63 | 40 | 95 | | 35 | CHB between H and H′ | |
| 11 | 90 | 45 | 90 | 25 | 45 | 2:1 and CHB between H and H′ | |
| 12 | 88 | 44 | 140 | 125 | 55 | 2:1 within H and H′ | VR 45 to 70/min during CHB |
| 13 | 100 | 54 | 80 | | 90 (H-V) | CHB distal to H | CHB to 2:1 |
| 14 | 82 | 46 | 130 | | 40 | CHB between H and H′ | |
| 15 | 78 | 42 | 250 | | | CHB distal to H | |
| 16 | 80 | 37 | 115 | | 40 | CHB between H and H′ | VR 37 to 41/min |

*Abbreviations:* CHB, complete heart block; VR, ventricular rate.

## Effects of intravenous atropine on AV conduction

Intravenous atropine sulphate (1 to 2 mg) was used on 9 occasions in 8 patients. In 2 patients with second degree AV block, improved AV conduction was seen, from 2:1 to 3:2 AV conduction in 1 patient (Case 4), and from 2:1 to 1:1 in the other (Case 5). In another patient (Case 3) with second degree block, no change in the AV conduction was seen after atropine administration at the time of initial investigation; however, a worsening of AV conduction from 2:1 to 3:1 occurred when atropine was given again 20 months later. No change or an inadequate response was seen in 3 of the 5 patients with complete heart block (Cases 8, 9, and 16), and only one patient (Case 12) showed a more than 20 per cent increase from the resting ventricular escape rate; in the fifth patient with complete heart block (Case 13), 2:1 AV conduction appeared after atropine administration. In summary, the effect of atropine on AV conduction and ventricular escape rate in this group of patients was variable and unpredictable.

## Follow-up and mortality

Twelve patients had permanent cardiac pacemakers implanted within one month of initial evaluation. Pacemakers were advised in all patients but 4 refused. The indications for pacemaker insertion were as follows: congestive heart failure in 4, syncope in 4, syncope and congestive heart failure in 2, and as a prophylactic measure in 2 patients. Ten patients died during the follow-up period. The deaths occurred between 1 and 31 months from the time of initial assessment. Seven of these 10 patients had permanent pacemakers at the time of death. Five deaths were from non-cardiac causes. There were 2 sudden deaths and in one of these who had a permanent pacemaker, pacemaker malfunction was suspected. Three deaths occurred outside hospital and the exact cause of death was not determined. In the 6 living patients, 5 with permanent pacemakers, the follow-up period has ranged from 3 to 58 months.

## Comments

Block within the His bundle was first described by Narula and Samet (1970) using the technique of His bundle electrography. They labelled the proximal and distal His bundle potentials as H and H′, respectively, and introduced the term 'split His potential'. After the initial description of this interesting electrophysiological entity by Narula and Samet (1970), several electophysiological, pathological, and experimental investigations of block within the His bundle were reported (Rosen

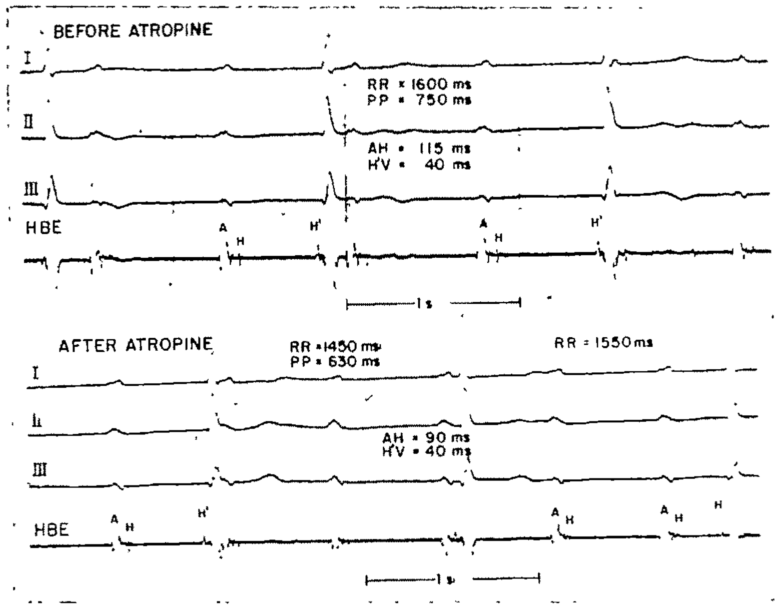

FIG. 2 *His bundle electrograms from Case 16 before and after intravenous atropine. There is complete block within the His bundle, persisting after atropine administration. The ventricular rate increases from 37 to 41/min. Shortening of the AH interval after atropine administration is also seen.*

*et al.*, 1970, 1971, 1972, 1973; Schuilenburg and Durrer, 1972; Gupta *et al.*, 1972, 1973; Bharati *et al.*, 1974; Narula and Samet, 1974; El-Sherif, Scherlag, and Lazzara, 1974). Various patterns may be seen on the His bundle electrogram, depending upon the level of block within the His bundle. If block is in the proximal part of the His bundle adjacent to the AV node, the His bundle electrogram resembles AV nodal block and split His bundle potentials are not present. However, if block is located in the middle part of the His bundle, a typical split His potential is recorded, with H and H′ denoting the activity of the proximal and distal segment of His bundle. Lastly, if the distal part of the His bundle is involved, no H′ is recorded and block occurs distal to the H potential in the presence of narrow QRS complexes.

## Aetiology

Although the majority of patients with His bundle block are elderly and have evidence of arteriosclerotic or degenerative heart disease, this type of block has also been seen in patients with congenital AV block, surgically induced AV block, block as a result of trauma to the heart, during acute myocardial infarction, and during cardiac catheterization (Rosen *et al.*, 1970, 1971, 1972; Jacobson and Scheinman, 1974; Nasrallah, Gillette, and Mullins, 1975). In a pathological investigation by Bharati *et al.* (1974), discrete lesions within the His bundle were seen in 2 patients who had shown split His bundle potentials with block during their life. In another pathological study, Lev *et al.* (1976) found extensive fibrosis of the His bundle and bundle-branches in a young patient who had sustained a stab wound of the heart 3 years before death and had shown a split His bundle potential with block during life. The electrophysiological pattern of His bundle block with classical split His potential has also been produced experimentally by ligating the septal branch of the left anterior descending artery in dogs (El-Sherif *et al.*, 1974).

## Clinical and electrocardiographic features

The average age of 76 years in our series was comparable to that of 74 years in the series of Narula and Samet (1974) and 70 years in the series of 7 patients reported by Rosen *et al.* (1973).The 64 per cent incidence of female patients in our series was less than the 84 per cent incidence reported by Narula and Samet (1974). The majority of patients in our series had significant associated cardiac disease which could explain the higher mortality we observed.

Although the initial description of block within the His bundle stressed the presence of narrow QRS complexes, block within the His bundle has also been seen in patients with wide QRS complexes. Of Narula and Samet's (1974) 37 patients, 35 had narrow QRS complexes. In contrast, 6 of our 16 patients had wide QRS complexes. Rosen *et al.* (1973) found that 4 out of 7 patients with His bundle block had wide QRS complexes. Both patients reported by Bharati *et al.* (1974) had wide QRS complexes in the escape beats, while 1 of the 4 patients reported by Schuilenburg and Durrer (1972) had wide QRS complexes. In our series, the AH interval was greater than 140 ms in 4 patients. Thus, in our experience disease of the AV node and bundle-branches may quite frequently accompany His bundle disease. The average ventricular escape rate of 41/min seen in our patients with complete heart block was comparable to that reported by Narula and Samet (1974) and Rosen *et al.* (1973).

The effect of intravenous atropine on conduction within the His bundle and on the His bundle pacemaker rate has been studied by different authors with variable results (Schuilenburg and Durrer, 1972; Gupta *et al.*, 1972, 1973; Narula and Samet, 1974; Nasrallah *et al.*, 1975). Narula and Samet (1974) found a mean increase of only 2 beats per minute in the ventricular escape rate after 2 mg intravenous atropine in patients with complete His bundle block. The effect of atropine on His bundle conduction and ventricular escape rate was variable and unpredictable in our series. Our observations are in agreement with those of Schuilenburg and Durrer (1972) and Nasrallah *et al.* (1975). Since some patients with His bundle block do show improvement in the AV conduction and slight increase in the His bundle escape rate, the possibility of parasympathetic influence on His bundle function cannot be ruled out.

## Follow-up and pacemaker therapy

It has been the policy at this institution to recommend permanent pacemakers to all patients who have shown evidence of block within the His bundle. This is partly based on our observation that patients with His bundle block more frequently have symptoms, including syncope, than patients with AV nodal block (Rosen *et al.*, 1973). Furthermore, in 2 patients in our series, second degree block progressed to complete heart block during the follow-up period. In our series, 12 patients received permanent pacemakers and 4 refused. Ten patients died during the follow-up period and of these, 7 had pacemakers at the time of their death. Five deaths were as a result of causes other than heart disease. One of the 2 patients who died suddenly was without pacemaker, and pacemaker malfunction was suspected in the other. Six living patients, 5 with permanent pacemakers, have been followed from 3 to 58 months.

In conclusion, our study shows the following:

1. Block within the His bundle, though a distinct electrophysiological entity, is frequently accompanied by disease of the AV node and bundle-branches.
2. Patients with chronic His bundle block are more often women, and the majority of these patients have significant accompanying heart disease.
3. Atropine administration has no definite effect on His bundle conduction and on His bundle pacemaker activity.
4. Since the majority of these patients are symptomatic and progression from lower degree block to higher degree occurs, a permanent pacemaker is recommended in these patients.

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# Monophasic action potentials of right atrium and electrophysiological properties of AV conducting system in patients with hypothyroidism

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*In 12 patients with manifest hypothyroidism right atrial monophasic action potentials showed a significant prolongation in comparison with data from normal or euthyroid patients. Atrial effective refractory periods were also significantly prolonged. After thyroid treatment the monophasic action potential duration and the effective refractory period of the right atrium were within normal ranges.*

*In 6 hypothyroid patients studies of AV conduction with the aid of His bundle electrography and atrial pacing showed a supraHisian conduction delay which was manifest in one case and latent in another two. InfraHisian conduction delay was encountered in 2 cases.*

Experimental studies have shown significant effects of the thyroid hormone on atrial muscle: a shortening of the repolarization phase of the action potential (Freedberg, Papp, and Vaughan Williams, 1970; Vaughan Williams, 1970), a shortening of the effective refractory period, and a reduction in the diastolic stimulation threshold as compared to euthyroid atria (Arnsdorf and Childers, 1970). An increased rate of diastolic depolarization in the sinoatrial node from thyrotoxic atria has also recently been shown (Johnson, Freedberg, and Marshall, 1973). Hypothyroidism had the opposite effects.

Only limited data exist concerning electrophysiological properties of the AV conduction system during hypothyroidism. The PR interval is usually normal in hypothyroidism though occasionally it may be prolonged (Bellet, 1971). Delayed AV conduction or complete AV block have been also reported (Ibrahim, 1957).

With the introduction of monophasic action potential (MAP) recording (Olsson, 1971; Brorson, 1975), a method has become available for the study of de- and repolarization phenomena in the cardiac muscle *in situ*, the results of which can be compared with data from studies with intracellular electrodes (Hoffman *et al.*, 1959).

In this paper we report our findings in patients with hypothyroidism in whom electrophysiological properties of the right atrium were investigated with the aid of MAP recordings. In addition, atrial pacing and His bundle electrograms were used to study the AV conduction system.

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## Subjects and methods

Twelve patients, 9 women and 3 men, aged between 35 and 54 years, were studied. All had clinical signs of hypothyroidism and low values of the total serum thyroxine (Seligson and Seligson, 1972). All maintained normal sinus rhythm and were without heart failure. None of them was under treatment with cardioactive drugs and no premedication was given before the investigation. After informed consent, MAP recordings were obtained with a bipolar suction electrode catheter passed percutaneously to the right chambers of the heart using a previously described technique (Gavrilescu *et al.*, 1972a, b). A bipolar pacing electrode was introduced via the brachial or femoral vein into the right atrium. A specially constructed battery-powered pulse generator was used to pace the atrium and for testing the refractoriness of the atrial tissue with the extrastimulus method (Wit *et al.*, 1970). The basic pacing cycle was 700 ms, and extrastimuli with a strength twice that of the diastolic threshold were delivered after each eighth beat. The Fig. shows an example of the determination of the atrial effective refractory period (AERP). MAP recordings were obtained from the mid right

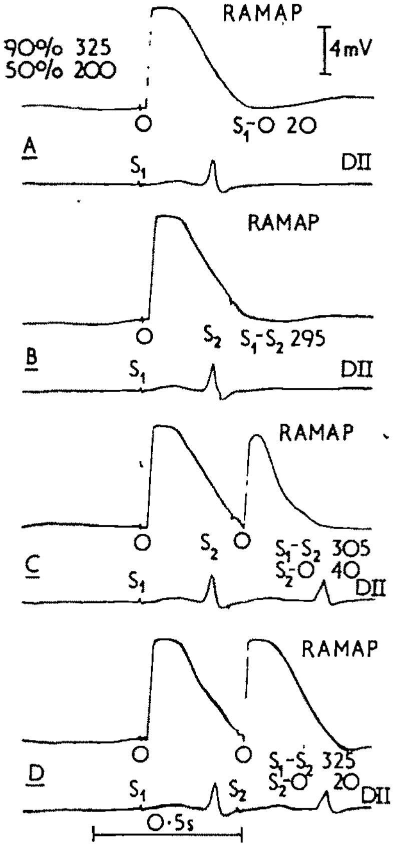

FIG. *Case 4 (Table 1). Right atrial monophasic action potential recording (RAMAP) showing the determination of the effective refractory period of the atrium. $S_1$, driving stimulus; $S_2$, testing stimulus. In B, $S_1$-$S_2$ of 295 ms represents the longest interval in which $S_2$ is not followed by an atrial response (AERP). (C) shows the atrial response during relative refractory period, and (D) shows the full recovery of atrial excitability.*

atrium in order to avoid variations caused by the position of the electrode. At least 10 MAP complexes were measured and the mean values determined. The MAP complexes were analysed according to Olsson (1971) and Brorson (1975). The MAP duration was measured at 90 per cent and 50 per cent repolarization, and from these values a measure of the relative repolarization rate during phase 3 (RRR ph 3) was calculated and expressed in per cent/s (Olsson, 1971).

Atrial MAPs were acceptable if the amplitude exceeded 8 mV, the course of the repolarization was smooth and was not distorted by the QRS deflection, and was stable for at least 20 seconds. The accuracy of the measured intervals was within 5 ms. This was determined by repeated measurements made by the same observer, and by independent measurements made by different observers.

In 7 patients the recordings were repeated after 3 to 4 weeks of thyroid treatment. In 6 patients in addition to MAP studies, His bundle electrograms were recorded using a tripolar electrode, introduced via the right femoral vein (Scherlag *et al.*, 1969). The conduction intervals were measured during sinus rhythm and during atrial pacing up to rates of 160 beats per minute.

The values obtained in hypothyroid patients were compared with MAP recordings and AERP determinations obtained in a similar manner in 12 normal subjects, with normal total serum thyroxine values, aged between 32 and 55 years.

## Results

Table 1 shows the results of the MAP recordings in the hypothyroid patients before and after thyroid treatment. Table 2 shows the data from the normal group. The hypothyroid state is associated with a significant lengthening ($P < 0·05$) of MAP duration at 90 per cent and 50 per cent repolarization and of the AERP in comparison with the normal group or hypothyroid treated patients. There are no significant differences between the control group and hypothyroid patients after thyroid treatment. Atrial RRR ph 3 showed no significant differences in the three groups studied.

Table 3 shows the results of the His bundle recordings. AV conduction was normal in sinus rhythm in 3 of the 6 studied patients. One patient (Case 11, Table 1) had first degree AV block at the supraHisian level, while 2 patients (Cases 1 and 6, Table 1) had HV interval prolongation. With atrial pacing AH interval increased progressively in 3 patients (Cases 6, 9, and 11, Table 1), Wenckebach periods occurred at a rate of 150 and 110 per minute, while in the other 3 patients 1:1 AV conduction took place up to a heart rate of 160 per minute. These changes suggest a latent conduction disturbance in the atrionodal area in Cases 6 and 9.

## Discussion

In a former paper from our laboratory (Cotoi *et al.*, 1972a) a lengthening of right atrial MAP in patients with myxoedema and a significant shortening after thyroid treatment was noted. However, there were also important variations in heart rate which was slow in patients with hypothyroidism and faster

TABLE 1 *Paced right atrial monophasic action potential (RAMAP) recordings in 12 patients with hypothyrcidism (cycle length 700 ms) before and after thyroid treatment.*

| *Case No.* | *Age (y) and sex* | *Before thyroid treatment* | | | | | *After thyroid treatment* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Total serum thyroxine (µg/100 ml)* | *RAMAP duration* | | *RARRR ph 3 %/s* | *AERP (ms)* | *Total serum thyroxine (µg/100 ml)* | *RAMAP duration* | | *RARRR ph 3 (%/s)* | *AERP (ms)* |
| | | | *90% Repolarization (ms)* | *50% Repolarization (ms)* | | | | *90% Repolarization (ms)* | *50% Repolarization (ms)* | | |
| 1 | 37 F | 0 50 | 335 | 270 | 615 | 310 | 5 27 | 266 | 158 | 370 37 | 243 |
| 2 | 44 F | 0·47 | 270 | 200 | 533 | 240 | — | — | — | — | — |
| 3 | 36 F | 0·43 | 300 | 174 | 317 | 280 | 4 93 | 252 | 164 | 454·55 | 235 |
| 4 | 35 F | 2·89 | 325 | 200 | 533 | 295 | 6·87 | 258 | 160 | 408·16 | 230 |
| 5 | 42 M | 3·43 | 280 | 200 | 500 | 270 | — | — | — | — | — |
| 6 | 40 F | 2 27 | 245 | 150 | 421 | 225 | 5·03 | 240 | 140 | 400·00 | 220 |
| 7 | 53 M | 3·15 | 315 | 206 | 367 | 290 | 4 97 | 260 | 150 | 363 64 | 240 |
| 8 | 50 F | 0 29 | 280 | 180 | 400 | 270 | — | — | — | — | — |
| 9 | 47 F | 0·32 | 300 | 230 | 571 | 275 | 4·11 | 255 | 160 | 421·05 | 238 |
| 10 | 49 F | 3·36 | 280 | 198 | 488 | 260 | 4·75 | 250 | 153 | 412·37 | 232 |
| 11 | 54 M | 0·40 | 285 | 210 | 533 | 260 | — | — | — | — | — |
| 12 | 46 F | 0 27 | 294 | 176 | 347 | 265 | — | — | — | — | — |
| Mean | | 1·78 | 292·4 | 199·5 | 468·8 | 270 0 | 5·13 | 254 4 | 155·0 | 404 3 | 234 0 |
| SD | | 0·52 | 7·8 | 9 3 | 30 0 | 7 3 | 0·52 | 7·8 | 9 3 | 30 0 | 7·3 |
| SE | | 0·41 | 7 2 | 8 7 | 27 6 | 6 7 | 0·32 | 3·1 | 3 0 | 11·7 | 2 9 |
| No. | | 12 | 12 | 12 | 12 | 12 | 7 | 7 | 7 | 7 | 7 |
| Significance at | | 0·05 | | | | | | | | | |
| | | S | S | S | NS | S | | S | S | NS | S |

*Conversion factor from Traditional to SI Units:* Thyroxine: 1µg/100 ml≈78·8 mmol/l.
RARRR=Right atrial relative repolarization rate: AERP=Atrial effective refractory period.

TABLE 2 *Paced right atrial MAP recordings in 12 normal subjects (cycle length 700 ms)*

| *Case No.* | *Age (y)* | *Sex* | *Total serum thyroxine (µg/100 ml)* | *RAMAP duration* | | *RARRR ph 3 (%/s)* | *AERP(ms)* |
|---|---|---|---|---|---|---|---|
| | | | | *90% Repolarization (ms)* | *50% Repolarization (ms)* | | |
| 1 | 46 | F | 6 3 | 255 | 167 | 454 55 | 240 |
| 2 | 32 | M | 5 8 | 226 | 132 | 425·53 | 230 |
| 3 | 37 | M | 7·6 | 270 | 158 | 357·14 | 255 |
| 4 | 41 | F | 8·0 | 276 | 165 | 360·36 | 260 |
| 5 | 43 | F | 6 9 | 245 | 150 | 421·05 | 235 |
| 6 | 47 | M | 7 9 | 237 | 143 | 425·53 | 225 |
| 7 | 51 | F | 8·5 | 263 | 153 | 363·64 | 253 |
| 8 | 54 | M | 5·7 | 232 | 140 | 434 78 | 227 |
| 9 | 35 | F | 5·9 | 240 | 138 | 392·16 | 230 |
| 10 | 48 | F | 8·8 | 266 | 160 | 377·36 | 248 |
| 11 | 55 | F | 8 4 | 270 | 165 | 380·95 | 256 |
| 12 | 50 | M | 6 9 | 228 | 135 | 430·11 | 225 |
| Mean | | | 7·2 | 250 7 | 155 0 | 401·9 | 240 3 |
| SD | | | 0·68 | 7·2 | 8 7 | 31·7 | 8 6 |
| SE | | | 0·23 | 4·3 | 3·7 | 10 3 | 3·2 |
| No. | | | 12 | 12 | 12 | 12 | 12 |

*Conversion factor from Traditional to SI Units:* Thyroxine: 1 µg/100 ml≈78·8 mmol/l.
Abbreviations as for Table 1.

TABLE 3 *Main electrocardiographic data and results of His bundle studies during sinus rhythm and right atrial pacing in 6 patients with hypothyroidism*

| *Case No. (Table 1)* | *HR* | *ECG data* | *His bundle electrogram* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Interval* | *SR* | *Paced cycle level* | | | | | | | |
| | | | | | *700* | *650* | *600* | *540* | *500* | *400* | *375* | |
| 1 | 65 | Low voltage<br>RBBB<br>PR=170 ms | AH | 90 | 110 | 145 | 160 | 170 | 180 | 210 | 220 | |
| | | | HV | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | |
| 2 | 68 | ST<br>PR=150 ms | AH | 90 | 110 | 135 | 145 | 160 | 170 | 175 | 180 | |
| | | | HV | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | |
| 6 | 58 | Low voltage<br>LAH<br>PR=180 ms | AH | 80 | 80 | 100 | 170 | 200 | 230 | 240 | — | AV block Wenck, 3/1 |
| | | | HV | 70 | 70 | 70 | 70 | 70 | 70 | 70 | — | |
| 8 | 59 | ST<br>PR=130 ms | AH | 60 | 60 | 70 | 80 | 80 | 90 | 100 | 120 | |
| | | | HV | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | |
| 9 | 63 | Low voltage<br>PR=175 ms | AH | 100 | 130 | 180 | 230 | 280 | — | — | — | AV block Wenck. 4/1 |
| | | | HV | 50 | 50 | 50 | 50 | 50 | — | — | — | |
| 11 | 66 | ST<br>PR=220 ms | AH | 150 | 180 | 210 | 220 | 250 | — | — | — | AV block Wenck, 3/1 |
| | | | HV | 50 | 50 | 50 | 50 | 50 | — | — | — | |

AV block Wenck. 3/1 or 4/1: second degree AV block with Wenckebach periods 3/1 or 4/1; LAH, left anterior hemiblock; RBBB, right bundle-branch block; ST, non-specific ST changes.

after treatment with thyroid hormone. Atrial refractoriness was not studied on that occasion. In the present study an entirely new group of patients was investigated. It was assumed that in agreement with the experimental data (Freedberg *et al.,* 1970) a prolonged action potential and refractoriness of the atrial muscle might explain the low frequency of atrial arrhythmias during hypothyroidism. Experimental data (Johnson *et al.,* 1973) have shown that the increase in the stimulation rate of the atria in euthyroid and hypothyroid rabbits is associated with a decrease in the 50 per cent repolarization time which was inversely related to the stimulation frequency. The atria from thyrotoxic animals tended to develop arrhythmias if stimulated more than 30 per cent above their intrinsic rates.

In our study a significant prolongation of right atrial MAP and of AERP was found during the hypothyroid state. These findings are in agreement with experimental studies showing a prolonged action potential and refractoriness in hypothyroid atrial myocardium (Freedberg *et al.,* 1970; Arnsdorf and Childers, 1970; Johnson *et al.,* 1973). Though MAP duration and AERP were not identical, and strong correlations between these two parameters could not be shown in normal subjects (Gavrilescu *et al.,* 1972a, b; Brorson, 1975), a change in the same sense was noted in relation to the thyroid status. The differences between MAP duration and AERP can be the result of the differences of the recording site, nonuniform response, or other factors that may separately influence the duration of the action potential and refractoriness (Hoffman, Kao, and Suckling, 1957). We have selected cases without any obvious cardiac disease for study in order to appreciate the effects of hypothyroidism on the electrophysiological properties of the atrial muscle. The lengthening of MAP duration may be related to the ionic basis of repolarization and the direct influence of thyroid hormone on membrane conductance (Johnson *et al.,* 1973). An increase of the amplitude and overshoot of the action potentials from hypothyroid atrial fibres was found (Johnson *et al.,* 1973). We have not observed any evident change of MAP amplitude associated with the thyroid status; however, this parameter has limited value in MAP analysis (Olsson, 1971).

Changes in right atrial MAP duration in man have been described under the influence of antiarrhythmic drugs (Olsson, Brorson, and Varnauskas, 1973; Olsson, 1974) or in association with the tendency of atrial fibrillation to recur after successful conversion (Olsson, Cotoi, and Varnauskas, 1971; Cotoi *et al.,* 1972b). We believe that in interpreting right atrial MAP in normal and pathological conditions, the thyroid state must be taken into consideration.

The effects of thyroid state on AV conduction are also a matter of interest. The occurrence of atrial tachyarrhythmias with a rapid ventricular rate, which respond poorly to digitalis is a common feature of hyperthyroidism. Electrophysiological studies (Goel, Hanson, and Han, 1972) have shown a shortening of the AV conduction time and of the functional refractory period of the AV conduction system in hyperthyroid dogs while opposite changes were noted in hypothyroid animals. Experimental studies (El-Shahaway, 1974) with the aid of His bundle recordings have shown enhanced intracardiac conduction after thyroid hormone administration. AV conduction delay and intraventricular conduction defects have been reported in hypothyroid patients (Ibrahim, 1957) but there have been no electrophysiological studies of AV conduction in clinical hypothyrodism.

Our data show that in 2 of the 6 patients there was a latent conduction defect at the AV level, while another showed first degree AV block in sinus rhythm. InfraHisian conduction delay was encountered in 2 patients. One of them had right bundle-branch block and the other one had left anterior hemiblock. These findings suggest generalized impairment of conduction in the specialized His-Purkinje system in both patients. Their RP intervals on the surface electrocardiogram were within normal limits though the patient with left anterior hemiblock also had latent AV conduction disturbance, developing induced supraHisian block at a relatively low heart rate (120 beats per minute). It appears from our study that the AV conduction system may sometimes present a latent or manifest conduction defect in middle-aged patients with hypothyrodism and without clinical cardiac disease. The limited number of cases studied, and the lack of more analytical studies which might exclude other latent cardiac disease (coronary angiography, myocardial biopsy), make it difficult to generalize from these observations.

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# Thrombotic jamming of a tricuspid prosthesis

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This report describes malfunction of a Björk-Shiley (tilting disc) prosthesis in the tricuspid situation and the usefulness of echocardiography in its detection.

## Case report

The patient, a married woman, underwent closed mitral valvotomy for rheumatic mitral stenosis at the age of 45 years. Nine years later she developed disabling effort dyspnoea, recurrent ankle swelling, and excessive tiredness. She was found to have mitral re-stenosis and tricuspid valve disease. The mitral valve was replaced with a 27 mm Björk-Shiley (tilting disc) prosthesis and the tricuspid valve with a 31 mm Björk-Shiley prosthesis. Warfarin was continued. Twelve months later she complained of breathlessness on slight exertion, bilateral ankle swelling, and excessive tiredness. These features persisted in spite of digoxin and intensive diuretic therapy.

Examination revealed elevation of the jugular venous pressure (4 cm above sternal angle) with a slow 'y' descent. There was peripheral cyanosis and bilateral ankle oedema. Right brachial blood pressure was 150/90 mmHg (20·0/12·0 kPa). Atrial fibrillation was established, the resting ventricular rate being about 70/min. A long mid-diastolic rumble was audible in the tricuspid area. The prosthetic opening and closing clicks sounded normal in the mitral area but diminished in the tricuspid area. The tender liver was palpable three finger breadths below the costal margin.

Chest *x*-ray showed moderate cardiac enlargement with tricuspid and mitral prostheses in evidence.

Electrocardiogram confirmed atrial fibrillation and showed a ventricular rate of about 70/min, with digitalis effect.

A phonocardiogram confirmed the presence of a long mid-diastolic murmur in the tricuspid area. The opening and closing clicks of the tricuspid prosthesis were not clearly recorded but those of the mitral prosthesis were normal.

### Echocardiograms (Fig. 1A and B)

An echocardiogram from the tricuspid prosthesis showed multiple abnormal echoes in the region of the disc with limitation of disc excursion (D-E = 10 mm); the normal for a 31 mm Björk-Shiley valve is 25 mm. The echogram from the mitral prosthesis was normal.

### Cardiac catheterization (Fig. 2)

Simultaneous right atrial (RA) and right ventricular (RV) pressure traces showed an end-diastolic gradient of 17 mmHg (2·3 kPa) across the tricuspid prosthesis with right atrial hypertension (20/17 mmHg (2·7/2·3 kPa)). Contrast injected into the right atrium showed this chamber to be dilated and its emptying delayed.

### Operative findings

Surgical exploration of the tricuspid site was undertaken in May 1975. The Björk-Shiley disc was found to be held in the almost fully closed position by extensive thrombotic pannus on its atrial and ventricular surfaces (Fig. 3).

## Discussion

The diagnosis of obstruction to the tricuspid prosthesis was suggested by the slow 'y' descent in the jugular venous pulse, long tricuspid mid-diastolic rumble, and diminished intensity of the tricuspid prosthetic sounds. An echogram from the tricuspid prosthesis showed abnormal multiple echoes from the region of the disc, compatible with the presence of thrombus on its surface. The echocardiographic disc excursion was found to be

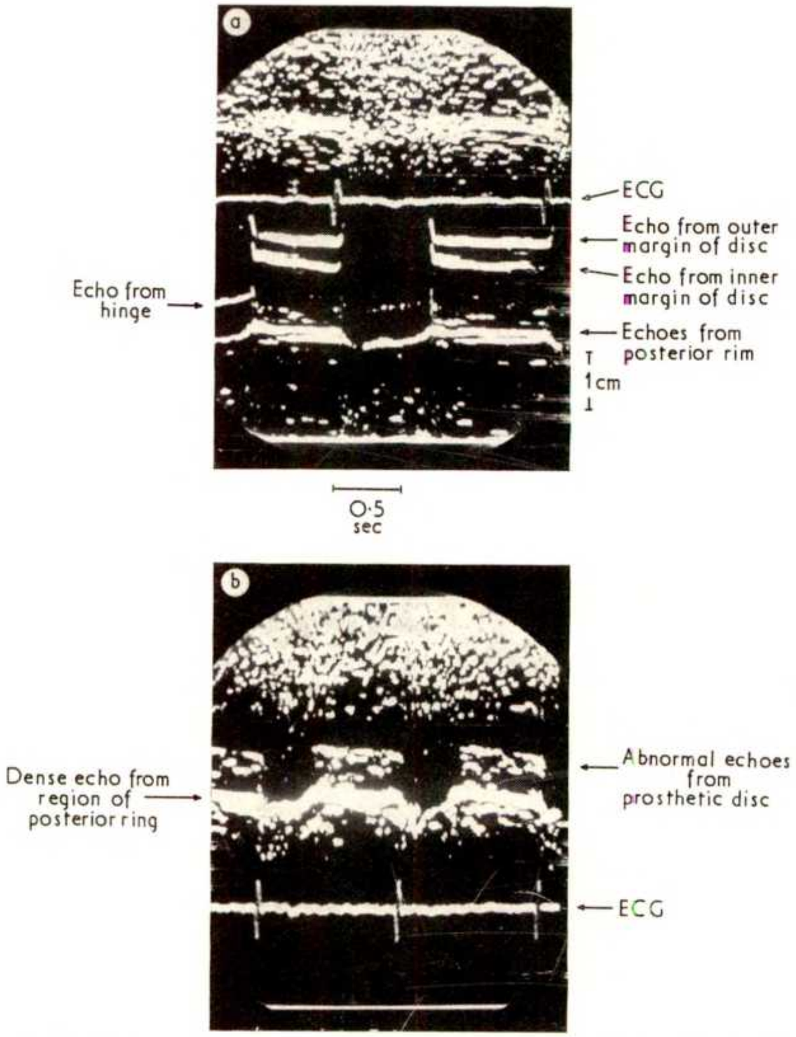
a
ECG
Echo from outer margin of disc
Echo from inner margin of disc
Echoes from posterior rim
1cm
Echo from hinge
0·5 sec
b
Abnormal echoes from prosthetic disc
Dense echo from region of posterior ring
ECG

FIG. 1 *(a) Echogram of the mitral Björk-Shiley (27 mm) prosthesis showing normal features: D-E = 25 mm, QRS to 'C' point = 40 ms; with disc opening (D-E) and closing movement (AC) being normal. (b) Echogram of the tricuspid Björk-Shiley (31 mm) prosthesis showing abnormal echoes in the region of the disc, its reduced mobility (D-E = 10 mm) and delayed closure (QRS—'C' point = 140 ms).*

reduced from the normal 25 mm to 10 mm. Cardiac catheterization and cardioangiography provided confirmatory evidence before excision of the malfunctioning prosthesis and its replacement with a biological valve.

Thrombotic jamming of a Björk-Shiley prosthesis in the tricuspid situation has not hitherto been reported. However, Samaan and Murali (1970), Vander Veer *et al.* (1971), and Bache *et al.* (1972) have documented the occurrence of life-threatening obstruction of Starr-Edwards' valves at this site in 9 patients. Obstruction became critical between 1 and 6 years after operation. A predisposing factor was considered to be present in every case, most commonly impingement on the right ventricular endomyocardium or secondary infection.

In this case a disc prosthesis became critically obstructed within 12 months in spite of well-

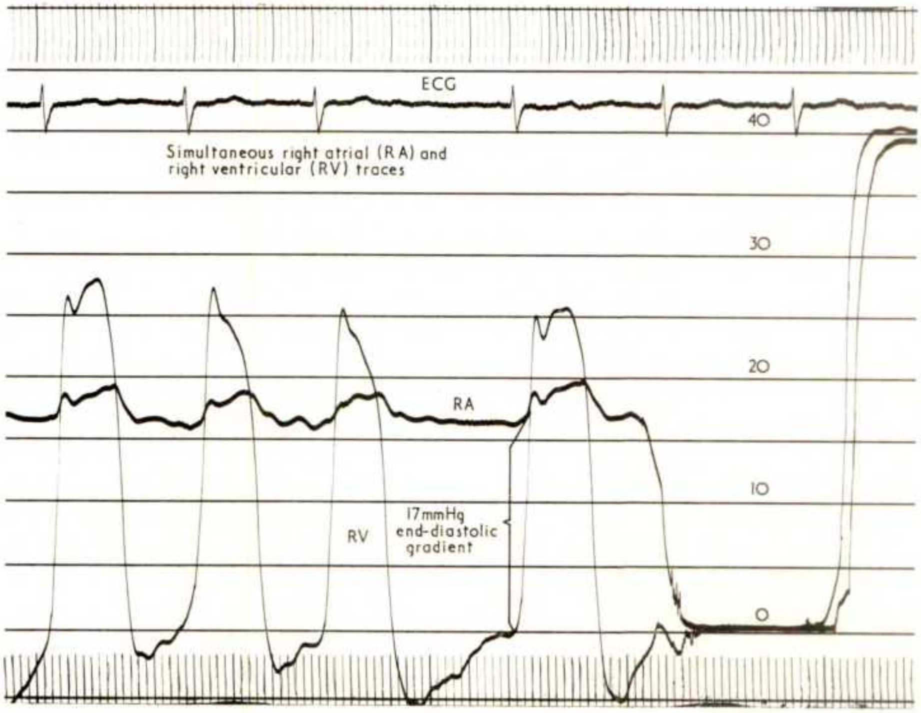

FIG. 2 *Simultaneous right ventricular (RV) and right atrial (RA) pressure traces showing end-diastolic gradient across tricuspid prosthesis.*

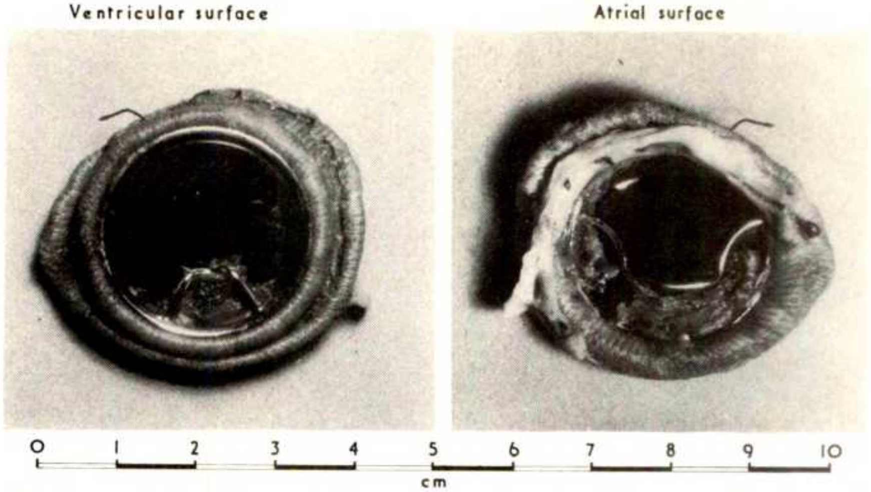

FIG. 3 *Removed Björk-Shiley prosthesis showing thrombus on the atrial and ventricular surfaces of the disc.*

controlled warfarin therapy and in the absence of any definable predisposing factor.

We thank Mr. B. B. Milstein for surgical help and permission to publish this case report.

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# Fatal outcome arising from use of a sutureless 'corkscrew' epicardial pacing electrode inserted into apex of left ventricle

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*A 59-year-old man is described in whom the insertion of an epicardial sutureless 'corkscrew' electrode resulted in fatal ventricular perforation. Fatal myocardial perforation can occur with this electrode and the apex of the left ventricle should never be used as the site of insertion. Necropsy also showed that the transvenous right ventricular electrode, inserted one year previously, had penetrated a tricuspid leaflet. This could have accounted for the ensuing pacing failure.*

## Case report

In June 1974, a 58-year-old man presented with fainting spells. He was hypertensive (220/120 mmHg), the fundi showing irregular arteries with venous nipping. His electrocardiogram indicated an inferior axis deviation, first degree block, complete right bundle-branch block, and deep Q waves in lead VI. In December of that year he developed complete heart block. A transvenous electrode was introduced without difficulty through a brachiocephalic vein, and satisfactorily positioned within the right ventricle. Pacing was achieved at a threshold of 0·7V. Nine months later, however, he again complained of dizzy turns. A 24-hour electrocardiographic tape-recording at that time showed periods of asystole, tachycardia, and extrasystoles (Fig. 1). It was assumed that the pacemaker was failing, and as there was no obvious displacement of the transvenous electrode on plain chest radiography, a new pacemaker was implanted into the original subcutaneous pocket. The previous electrode was left *in situ*. The threshold was again 0·7V. A subsequent report confirmed that there had been a premature battery depletion of the original pacemaker.

Soon after, he again complained of persistent dizzy spells and further electrocardiograms showed inconstant pacing. At that stage, as the result of the original battery failure was not known, it was thought best in the interest of the patient to replace the entire endocardial by an epicardial system.

In view of the reported number of 'corkscrew' electrodes used, the safety and simplicity of the procedure, and our own uncomplicated experience with this type of epicardial electrode, it was chosen as most suitable for the needs of this patient. His blood pressure on treatment at that time was 140/100 mmHg. The heart was approached through the fifth intercostal space. Using light pressure, the 'corkscrew' electrode was screwed into the apex of the left ventricle. At 2½ turns, arterial bleeding was noticed. The electrode was then gently unscrewed

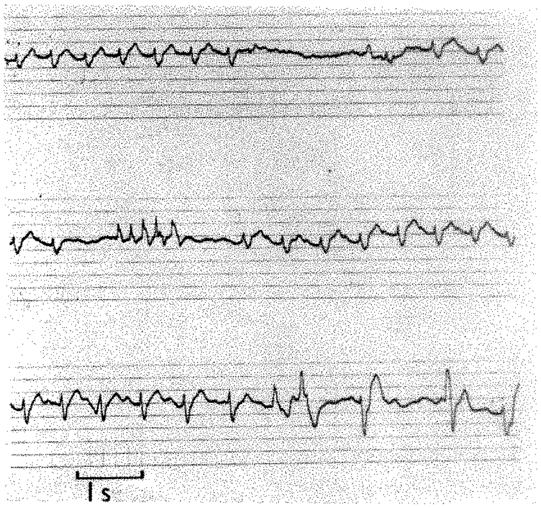

FIG. 1 *Non-consecutive strips from a 24-hour electrocardiographic tape-recording showing episodes of asystole, tachycardia, and extrasystoles.*

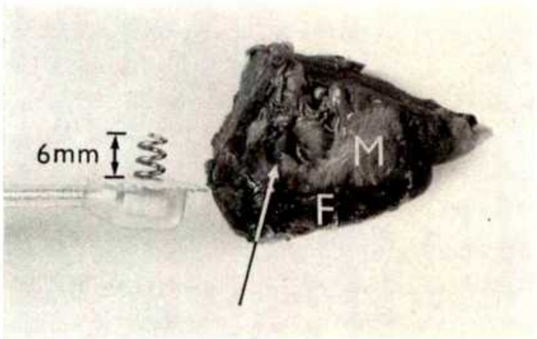

FIG. 2 *Necropsy specimen showing apex of the left ventricle situated inferiorly with the 'corkscrew' electrode at same magnification. The arrow marks the path of perforation. F represents epicardial fat, M myocardium.*

and the haemorrhage was seen to be caused by ventricular perforation. The bleeding was controlled by means of sutures and buttresses of Teflon felt. Further leakage, however, occurred, which required more extensive buttressing. A similar 'corkscrew' electrode was then implanted uneventfully 4 cm higher up on the lateral wall of the left ventricle. Ten minutes after closing the wound, there was a dramatic drop in blood pressure because of further rapid haemorrhage. The heart was re-exposed and more suturing was required to control the apical bleeding, but the patient failed to respond to resuscitative measures.

At necropsy the heart was greatly enlarged (660 g). There was left ventricular hypertrophy with a wall thickness of 1·8 cm over the outflow tract. At the apex of the left ventricle there was a perforation admitting a finger tip. This was the area where the first electrode had been implanted, and, at that site, the left ventricular wall surprisingly only measured 4 mm in thickness. There was also a superficial layer of epicardial fat measuring 5 mm.

The electrode itself was slightly longer (6 mm) than the apical myocardial wall (Fig. 2).

There was no evidence of myocardial infarction or focal fibrosis, though some endocardial fibrosis was noticed on the left aspect of the interventricular septum, and the anterior descending branch of the left coronary artery was narrowed to about 50 per cent of its diameter.

In the right side of the heart, the transvenous electrode had perforated the posteroinferior cusp of the tricuspid valve and was found to slide readily through a channel of organized fibrous tissue (Fig. 3).

## Discussion

The so-called sutureless 'corkscrew' epicardial pacing electrode[1] has been in use since 1971 (Hunter *et al.,* 1973; Mansour, Fleming, and Hatcher, 1973; Stewart, 1974; Naclerio and Varriale, 1974; Wolner, Stellwag, and Navrátil, 1975). By 1976, approximately 30 000 of these had been implanted

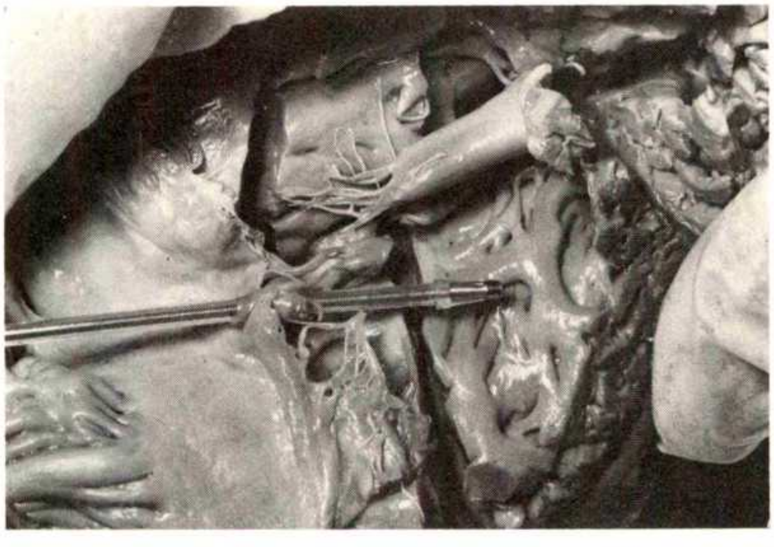

FIG. 3 *Necropsy specimen showing transvenous electrode perforating tricuspid leaflet. There is a fibrous tunnel at the site of perforation.*

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[1] Model 6917 Medtronic, Minneapolis, Minnesota.

world wide, 700 in the U.K. To date only 13 mechanical failures caused by fracture of the corkscrew coil have been reported as well as one coductor failure. This is in addition to a small percentage (4 to 5%) of recognized pacing problems such as exit block, occasional arrhythmias, or infection (J. P. Lawther, Medtronic UK, Slough, Berks, 1976, personal communication). It is generally accepted that complications occur less frequently with epicardial than endocardial systems (McConahay *et al.,* 1971; Dixon *et al.,* 1972; Mansour *et al.,* 1973). The advantages of using the 'corkscrew' type reside in the secure myocardial insertion, in the limited approach and ease of implantation which is well tolerated by patients, in the fact that the subxyphoid insertion can be performed under local anaesthesia, and that the pacing threshold is of a low magnitude.

The site of implantation of the electrode does not appear constant: some authors chose an area as close to the apex of each ventricle as possible (O'Neill and Spagna, 1974). Others suggest a 'healthy looking area of myocardium' without adding further precision (Mansour *et al.,* 1973). Others still recommend the inferior (Stewart, 1974; Roberto, 1974; Wolner *et al.,* 1975) or the anterior surface of the right ventricle (Naclerio and Varriale, 1974). These latter authors also suggest the choice of an area 'free of epicardial fat' whereas Stewart (1974) states that scarred areas of myocardium should be avoided.

Over the years, in the light of clinical trials and increasing experience, the chosen site of insertion has tended to be from the left to the right ventricle, the latter being an easier approach (J. P. Lawther, 1976, personal communication). Mansour reported 3 failures in 26 patients using this technique. One patient died from a myocardial infarction two weeks after operation, another had repeated ventricular tachycardia, and a third had a rising threshold. In Naclerio's series of 36 implantations, there were two deaths, one two months after operation from intractable congestive failure, and one from myocardial infarction after a major orthopaedic procedure. In the 30 cases of Wolner *et al.,* there were several complications. In one patient, the electrode became separated from the myocardium two hours after operation. This was thought to be the result of incomplete implantation and was rectified. One patient developed a high threshold and another an infection at the site of insertion. Two of their patients died, one from ventricular fibrillation and another from pneumonia. Stewart, Cohen, and Murphy (1975) described an instance in which the right ventricle was entered by a similar epicardial electrode, but the situation was controlled by suturing the site of the perforation. To the best of our knowledge, no other cases have been reported to date in which the 'corkscrew' electrode was shown to penetrate a ventricular cavity and lead to the death of the patient.

In a series of 25 hearts exposed, at necropsy, to twisting of the anterior surface of the right ventricle in a variety of areas, in no instance was there penetration of the coil into the ventricular cavity (Naclerio and Varriale, 1974).

Prompted by the above observation, one of us (J.W.B.B.) has recently examined 10 consecutive postmortem hearts. The thickness of the myocardium at the tip of the apex was never greater than 2 mm (to be published).

The pressure difference which exists between the two ventricles conceivably renders a left ventricular haemorrhage more liable to occur, particularly in the presence of a thin apical myocardium or in association with raised blood pressure. Excessive adipose tissue adds a further hazard by obscuring the state of the underlying myocardium and by making an accidental perforation more difficult to repair.

In view of these findings, and the fatal outcome described, we recommend that the 'corkscrew' electrode should not be inserted into the apex of the left ventricle, nor through abundant fat.

It seems likely that the tricuspid cusp perforation seen in our patient was partially responsible for his pacing failure, as the transvenous electrode could have been intermittently dislodged by the movement of the valve. There was no evidence in this patient, of adhesion to the tricuspid valve secondary to endocarditis (Friedberg and D'Cunha, 1969).

We thank Dr. E. M. M. Besterman and Mr. L. L. Bromley for allowing us to report this case.

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# Pseudo second degree atrioventricular block with bradycardia

## *Successful treatment with quinidine*

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*Pseudo second degree atrioventricular block resulting from blocked His premature beats was successfully treated with quinidine. The diagnosis was proved by His bundle electrogram which showed both blocked and conducted His premature beats. The blocked His prematures produced second degree atrioventricular block by making the atrioventricular junction refractory. Quinidine abolished both conducted and blocked His extrasystoles. There has been no recurrence of arrhythmia during a one-year follow-up.*

Langendorf and Mehlman (1947) suggested that non-conducted junctional premature beats might produce second degree atrioventricular block by blocking the sinus impulse following the premature beat. They suggested that the block was caused by junctional extrasystoles which were concealed because of both anterograde and retrograde block. Rosen, Rahimtoola, and Gunnar (1970) showed, with His Bundle recordings, second degree atrioventricular block resulting from blocked His premature beats. Since there was no intrinsic abnormality of the atrioventricular conduction, they called the resulting block, 'pseudo-block'.

We report here a patient with bradycardia resulting from pseudo second degree atrioventricular block caused by blocked His premature beats: he was successfully treated with quinidine.

### Case report

A 54-year-old man reported to the hospital complaining of tiredness and weakness. There was a history of heavy alcoholic intake, but the patient had discontinued drinking a few months before. There was no history of palpitation or dizziness. Physical examination revealed an irregular pulse, with a basic rate of about 70 beats a minute but with periodic slowing to almost 30 beats a minute. The blood pressure was 120/80 mmHg (16·0/10·6 kPa). There was no evidence of heart failure. The heart size was normal, no gallop rhythm was heard, and there were no murmurs. The remainder of the physical examination was normal. The electrocardiogram showed supraventricular premature beats with aberration and episodes of apparent Mobitz type II block (Fig. 1a). Apart from the arrhythmia, the electrocardiogram was normal. The patient was admitted for further evaluation and treatment of the arrhythmia. Initially he was given tincture of belladonna, 1 ml, four times a day. The premature beats as well as periods of apparent second degree atrioventricular block were uninfluenced by this therapy. His bundle recordings were then made to clarify the nature of the arrhythmia.

### Electrophysiological studies

The His bundle electrogram was recorded simultaneously with lead II of the surface electrocardiogram at a paper speed of 100 mm/s. Several hundred cardiac cycles were analysed. The majority of the beats recorded were sinus beats, with normal AH and HV intervals. The QRS complex of these sinus beats was normal in duration. Premature beats occurred at an average frequency of 3 to 5 per minute. These beats could be separated into two types according to the behaviour of the QRS complex. In the first type, there was a minor change in QRS morphology but without significant increase in its duration. The second type showed wide QRS complexes resembling ventricular ectopic beats. The simultaneous His electrogram, however,

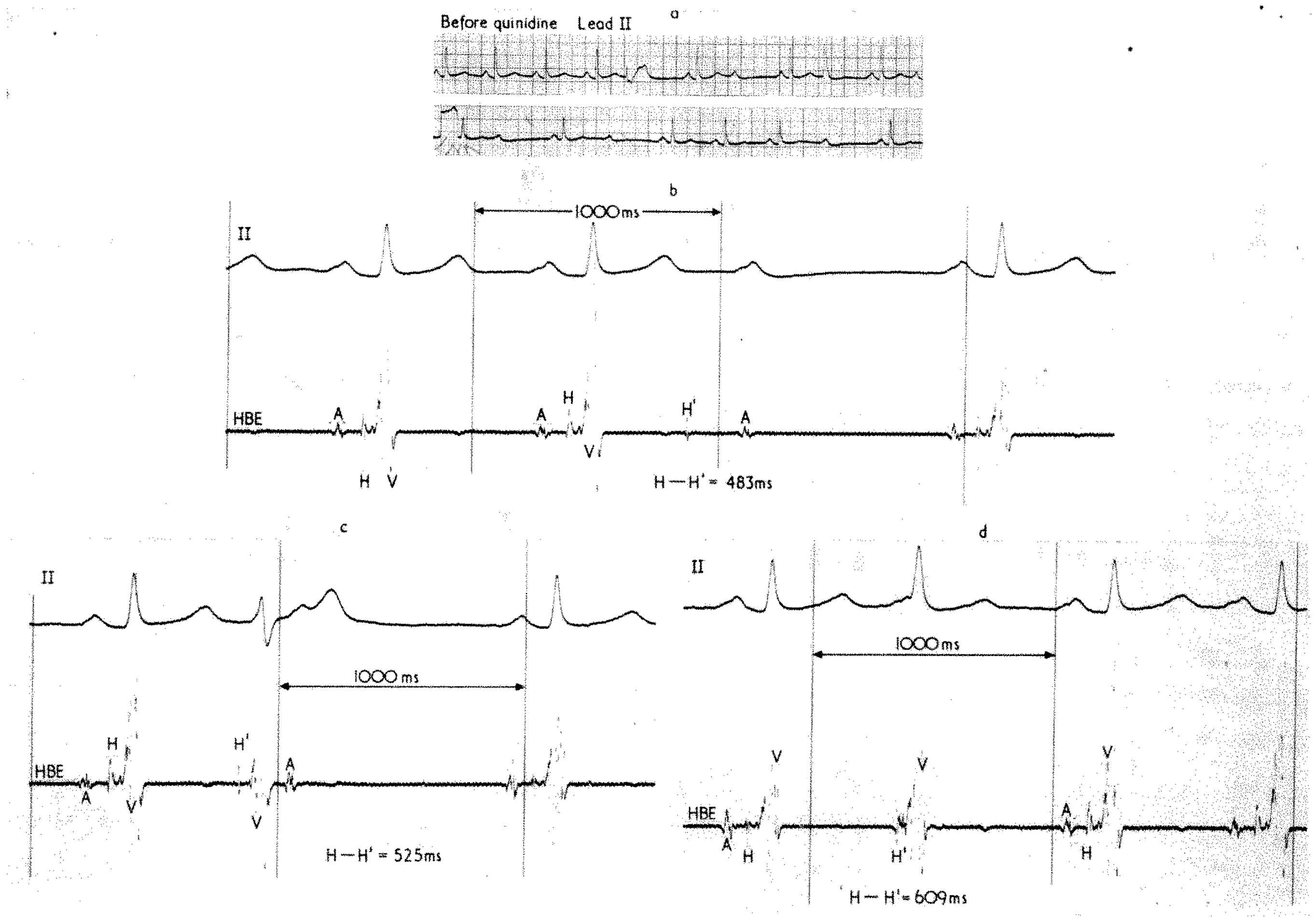

FIG. 1 *(a) Electrocardiogram before quinidine therapy. The top strip of the cardiogram shows premature beats with varying morphology of the QRS complexes. The second strip shows 2:1 atrioventricular block, followed by 3 conducted sinus beats with constant PR interval. The succeeding P wave is blocked producing type II second degree atrioventricular block. The His bundle electrogram (HBE) was recorded simultaneously with surface electrocardiogram at a paper speed of 100 mm/s. The recordings are labelled b, c, and d. (b) Apparent type II atrioventricular block is seen in the surface electrocardiogram. HBE shows H' with anterograde and retrograde block preceding the blocked atrial (A) deflection. (c) and (d) HBE clearly shows that the premature beats seen in the surface electrocardiogram are His extrasystoles conducted with varying degree of aberration since H' deflection precedes the V deflection of the premature beats. The A deflection representing the atrial activation by the sinus impulse follows the premature beat in (c). It is superimposed on H' of the premature beat in (d).*

showed a consistent presence of a His spike preceding the V deflection in both types of premature beats localizing their origin to the His bundle (Fig. 1c, d). These two types of premature beats were His extrasystoles, one type with slight and the other with more aberrant ventricular conduction. Periods of second degree atrioventricular block with non-conducted normal P waves occurred at frequency of about 10 a minute. The surface electrocardiogram showed that the block was type II in nature and occurred without a change in PR interval of the preceding sinus beats. At no time was more than one beat blocked in succession. His bundle recordings during these periods showed spikes preceding the blocked A deflection (Fig. 1b). The latter corresponded to the non-conducted normal P waves. As the patient had conducted His premature beats throughout the recording, it is reasonable to conclude that these spikes represented His premature beats with both retrograde and anterograde block. These spikes will be designated as H′. H′-A interval varied between 94 and 304 ms with an average interval of 212 ms. Every blocked sinus beat was preceded by H′. The behaviour of the His premature beat was determined primarily by the interval between the H spike of the preceding sinus beat and the H′. The His extrasystoles with short H-H′ intervals were blocked, while those with long H-H′ intervals were conducted with slight aberration. The H-H′ interval of the premature beats with greater degree of aberration fell between these 2 groups. These three types of His premature beats could clearly be separated into three groups, determined by the length of the H-H′ interval (Fig. 2).

## Hospital course

Quinidine sulphate, 200 mg, four times a day was given in an attempt to suppress the premature beats. Within 24 hours, the premature beats as well as periods of pseudo atrioventricular block were completely abolished and did not recur during a seven-day period of observation with continuous electrocardiographic monitoring (Fig. 3). Quinidine was then stopped, and within 12 hours the premature beats as well as the pseudo second degree atrioventricular block reappeared. The arrhythmia continued for 36 hours until quinidine therapy was restarted, at which time the arrhythmia again disappeared. During a one-year follow-up under quinidine therapy, there has been no recurrence of the arrhythmia.

## Discussion

This case is an interesting example of successful treatment of apparent second degree atrioventricular block with quinidine, a drug which normally would be considered contraindicated in atrioventricular block. It is important to recognize the 'pseudo' nature of the block. The diagnosis should be suspected when a patient presents with apparent type II atrioventricular block with narrow QRS complexes but who also shows junctional premature beats elsewhere in the electrocardiogram. The usual

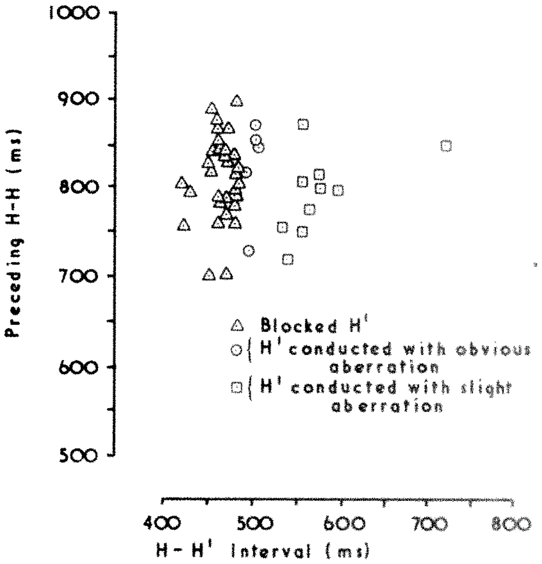

FIG 2 *The effect of timing of H′ on conduction to the ventricles. Abscissa: H-H′ intervals; Ordinate: preceding H-H intervals Note that His premature beats with short H-H′ interval are blocked while those with long H-H′ interval are conducted with slight aberration. His prematures with obvious aberration fall in between these two groups. The preceding H-H intervals do not appear to influence the behaviour of the His extrasystoles.*

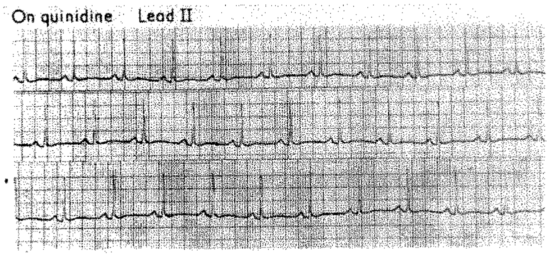

FIG 3 *The electrocardiogram recorded after quinidine therapy was started The premature beats as well as periods of second degree atrioventricular block are no longer present.*

settings for atrioventricular block, such as myocardial infarction and digitalis toxicity, may not be present. The presence of His premature beats showing both retrograde and anterograde block should be shown by His electrogram before embarking on a trial of quinidine.

In our patient, the reason for occurrence of His premature beats was not clear. They did not appear to be re-entrant beats, as the coupling interval varied. The premature beats occurred irregularly and did not appear to arise from a parasystolic focus. Blocked premature beats may arise from any part of the His-Purkinje system but the presence of conducted premature beats preceded by a His spike localized their origin to the His bundle. The interval between the H deflection of the preceding sinus beat and the H′ determined the conduction of the premature beats to the ventricles. With shorter H-H′ intervals the premature beats showed both retrograde and anterograde block, and consistently blocked the following sinus impulse by concealed conduction within the atrioventricular junction. We did not encounter any sinus beats conducted to the ventricles with prolonged AH interval following the blocked H′, as described by Rosen *et al.* (1970). The unique success of quinidine in abolishing the significant bradyarrhythmia in this patient eliminated the need for implanting a permanent pacemaker.

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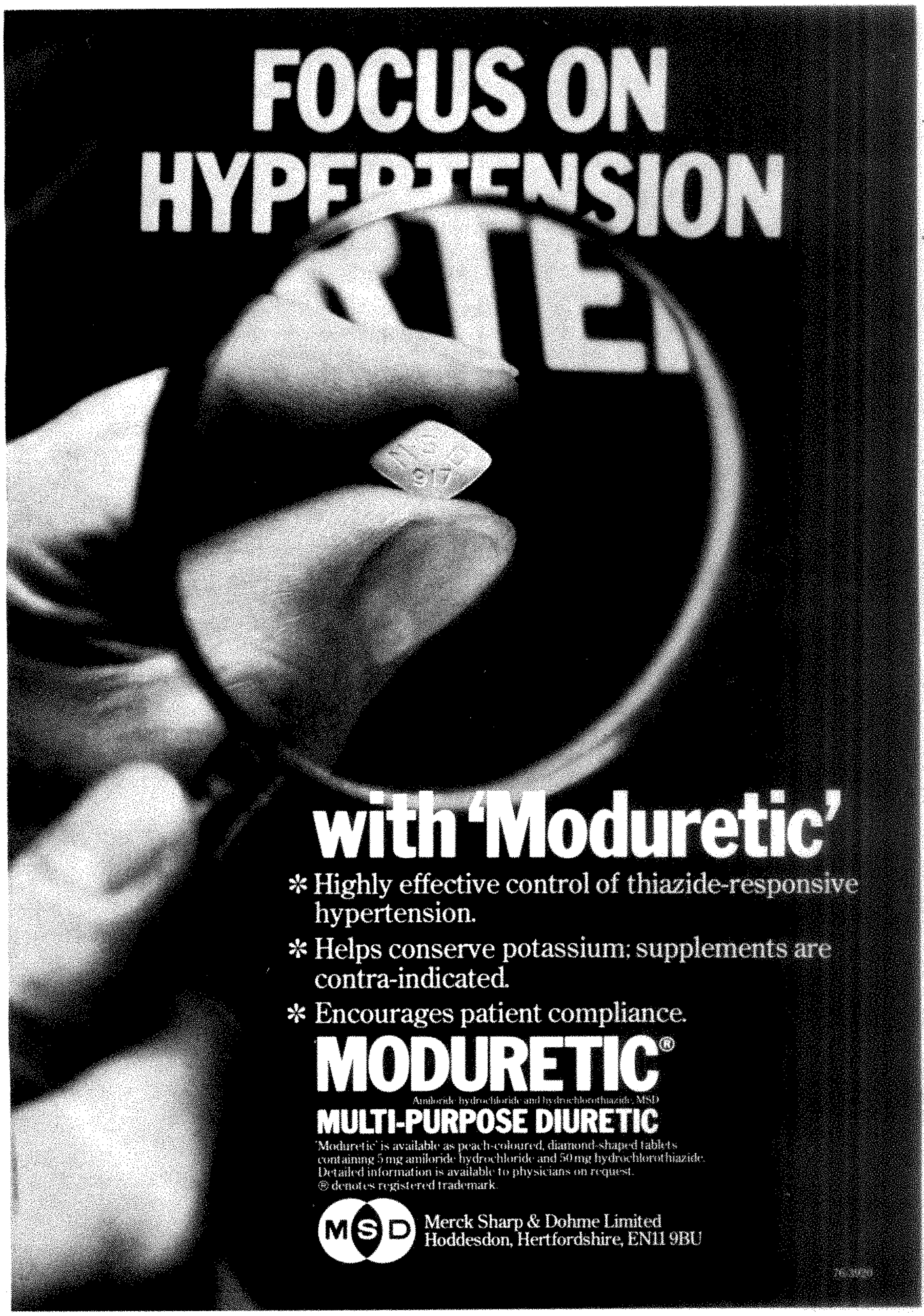

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"The rapid onset and short duration of action of loop diuretics are clearly desirable when a rapid diuresis is indicated, and when given in the evening to patients with chronic heart failure, the short duration of action can ensure a good nights sleep undisturbed by nocturia or breathlessness."9

"The use of potent and short-acting diuretics such as bumetanide allow the Physician and patient scope to decide upon the most appropriate time for administration and so reduce major disruptions in the patient's daily routine."10

"Patients who go out to work may find Burinex K given in the evening more socially acceptable."11

## Patients prefer Burinex K

"These results indicate that when long-term diuretic/potassium supplement therapy is required, Burinex K is a more acceptable regimen to the patients than one in which diuretic + Slow K are given separately."13

"Patients showed a highly significant preference to take two tablets on one occasion (Burinex K) rather than two different types of tablet on three separate occasions (Lasix + K)."14

* Burinex is a trade mark

℞ . . . But of course the decision is yours.

# Burinex K*

**Tablets contain 0.5 mg bumetanide with a slow release core of 573 mg (7.7mEq) of potassium chloride.**

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